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JUNE 1956

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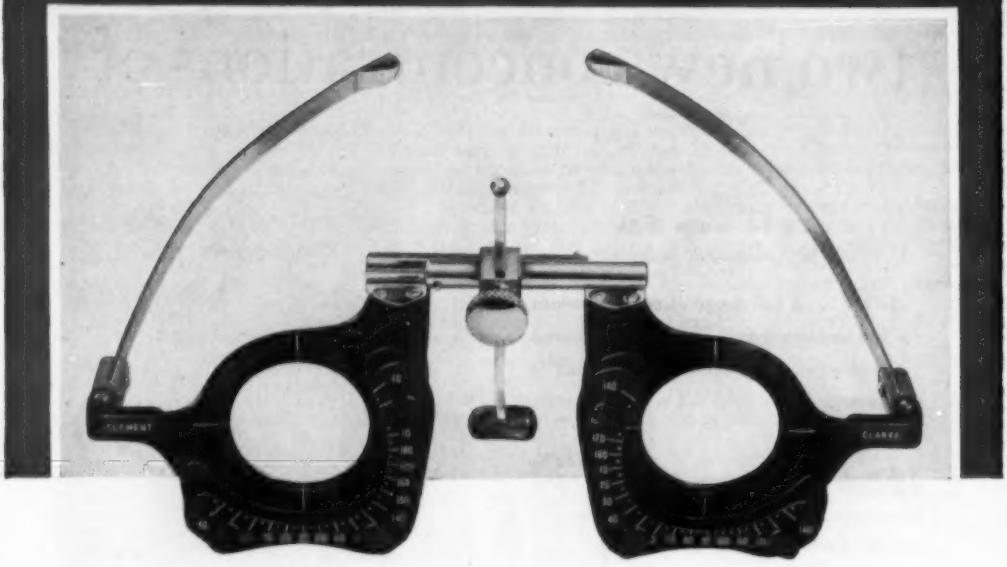

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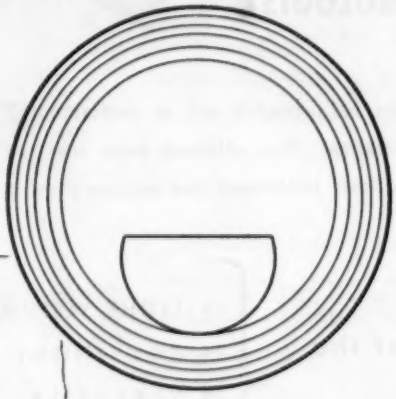

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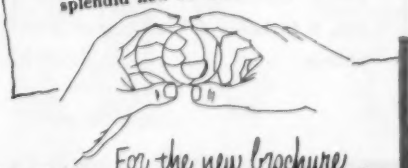

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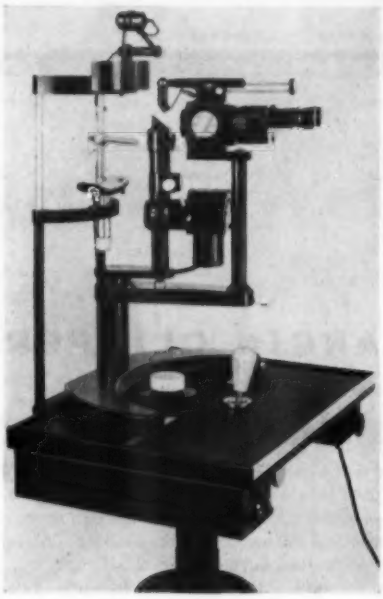

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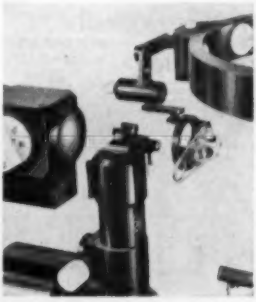

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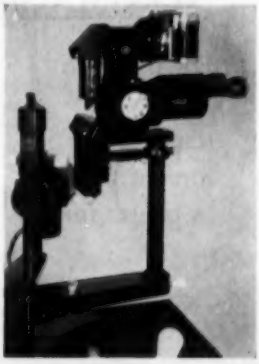

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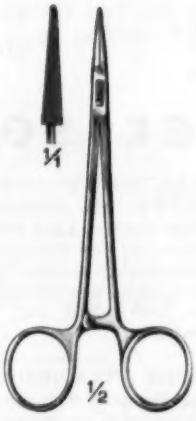

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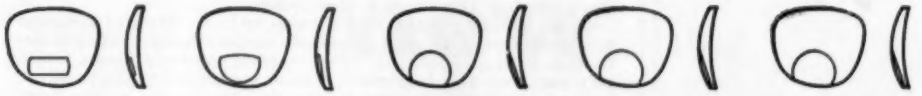

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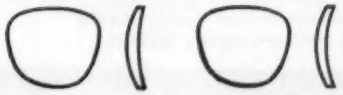

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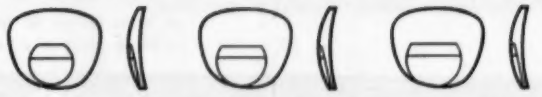

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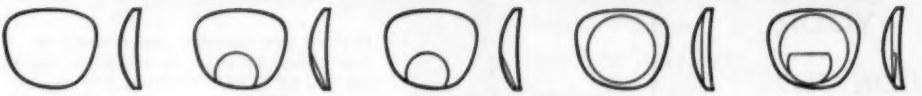

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1. Rasgorshek, R. H., and McIntire, W. C.: Am. J. Ophth. *40*:34 (July) 1955.
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Aqueous Humor Dynamics in Glaucoma

Effect of Ganglionic Blocking Agents and Thiopental Sodium (Pentothal) Anesthesia on Aqueous Humor Dynamics

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AND
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New York

The purpose of this paper is to study various factors that may influence the intraocular pressure in glaucoma and thereby obtain information concerning the etiology and pathogenesis of this disease. More specifically, this paper is concerned with the effect of ganglionic blocking agents and some central nervous system depressant drugs on aqueous humor dynamics in glaucomatous eyes. Primary glaucoma cannot be duplicated satisfactorily in the animal eye; therefore, its pathogenesis has to be investigated on human glaucomatous eyes. The tonographic method of Grant * was employed in the present work because it is a convenient research tool with which one can study the mechanism of ocular hydrodynamics in patients.

The use of ganglionic blocking agents in the treatment of hypertension has been well documented in the past few years; Paton,[3] Burt,[4] and Locket [5] described the mode of action of these agents in man, while their specific effect on the eye has been reported by Barnett,† Cameron,[6] and von Sallmann.‡ Ganglionic blocking agents cause irregular pupillary changes, disturbance in accommodation, and lowering of the intraocular pressure; the effect on vision was recently reported by Bruce.[9] The best known of these ganglionic blocking agents are the methonium compounds, particularly hexamethonium; the means by which these compounds lower the tension in human eyes is not known. Therefore, it was thought that by employing tonography one could elucidate the effect of these ganglionic blocking agents on aqueous humor dynamics in glaucomatous eyes.

The influence of the central nervous system on ocular hydrodynamics is still a controversial issue. Duke-Elder,[10] Magitot,[11] Thiel,[12] and others [13] have advocated

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* References 1 and 2.

† References 6 and 7.

‡ von Sallmann, L.: Personal communication.

for years that there are nerve centers regulating the tension of the eye. The recent experimental work of von Sallmann [14] and Lowenstein [15] clearly indicated that the diencephalon influences the intraocular pressure. Consequently, any drugs that are central nervous system depressants, such as the barbiturates, may be expected to affect the ocular tension. In order to learn more about the controlling influence of the central nervous system on ocular tension, intravenous thiopental sodium (Pentothal) anesthesia was administered to glaucomatous patients, and the resulting changes in aqueous humor dynamics were measured with tonography.

MATERIALS AND METHODS

For this study, eyes with chronic simple glaucoma were employed. Eyes with angle-closure or narrow-angle type glaucoma were purposely not utilized because it is known that in this type of glaucoma the size of the pupil and the state of the anterior chamber angle have a considerable influence on the intraocular pressure. Therefore, any effect produced by the compounds administered to these patients may be overshadowed by the pupillary changes and the state of the anterior chamber angle. On the other hand, in chronic simple or open-angle type of glaucoma, the size of the pupil and the width of the anterior chamber angle have probably only a minimal effect on the pressure-regulating mechanisms of the eye.

All patients had well-documented case histories of chronic simple glaucoma and had been followed in our glaucoma department for several months to several years. Their eyes had not been operated upon, and miotic medication was stopped for two days before the experiment. Also, when at all possible, patients with a relatively normal cardiovascular system were utilized, most of them having normal blood pressures. They were admitted to the hospital for these tests; the tensions were taken with the electronic tonometer, and tonography was carried out according to Grant's [16] four-minute test, all measurements being performed by the same observer. The facility of aqueous outflow as described by Grant is expressed as a coefficient, *C*, and is the reciprocal of the resistance to the outflow (cubic millimeters per minute per millimeter Hg pressure). Knowing the facility of outflow and the intraocular pressure, the total rate of aqueous flow, or *K*, was calculated and expressed in cubic millimeters per minute. The intraocular pressure was obtained from the latest tables supplied by the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology, published in 1954.

A. Hexamethonium.—De Long and Scheie [17] and Harris and associates [18] have demonstrated in animal eyes that Dibenamine, another adrenergic blocking agent, caused a decrease in the rate of aqueous formation. Because of its marked toxicity and severe side-effects, the use of Dibenamine is not advisable for humans. Therefore, hexamethonium,[21] being relatively safer to use, was chosen for our purposes. Hexamethonium chloride was injected either intramuscularly or retrobulbarly; the ocular tension and the blood pressure were measured, and the aqueous outflow test was performed both before and at varying time intervals after the administration of the drug. Preliminary work with hexamethonium indicated that the peak effect on the intraocular pressure is reached one hour after administration of this compound; therefore, tonography was usually carried out just before and about one hour after injection of the drug.

B. Thiopental Anesthesia.—Thiopental sodium (3.0% concentration) was administered intravenously to a group of patients with chronic simple glaucoma to obtain light surgical anesthesia; premedication was given about one hour before the thiopental anesthesia was started. To supplement the thiopental, nitrous oxide was also used in some of these patients; blood pressure and ocular tension were measured, and tonography was performed at varying time intervals before, during, and after the anesthesia. To study the effect of premedication only, a group of normal eyes were also employed; these patients were admitted to the hospital for cataract extraction, and tonography was carried out on these eyes before and after premedication with secobarbital (Seconal).

RESULTS

A. Hexamethonium.—Table 1 shows that in 23 eyes with chronic simple glaucoma 25 mg. of hexamethonium chloride injected intramuscularly caused an average drop of 13.2 mm. Hg in the intraocular pressure. Tonography results indicated

that this drop in intraocular pressure was due to a decrease in the rate of flow or formation of aqueous and that the facility of aqueous outflow remained approximately constant. At the same time, the blood pressure dropped only to a limited

TABLE 1.—*Effect of Intramuscular Injection of 25 Mg. of Hexamethonium on Aqueous Humor Dynamics of Patients with Chronic Simple Glaucoma Who Had Not Been Operated On and Had No Miotic Medication for Forty-Eight Hours Prior to the Test* *

	Before Injection				One Hour After Injection			
Eye	*C*	*K*	IOP	B. P.	*C*	*K*	IOP	B. P.
1	0.09	3.1	37	130/82	0.08	1.8	24	114/72
2	0.07	2.3	34	130/82	0.07	1.6	24	114/72
3	0.08	2.2	30	150/92	0.08	1.6	21	152/100
4	0.06	2.1	37	150/92	0.07	1.7	25	152/100
5	0.10	3.1	33	118/74	0.11	1.8	17	80/50
6	0.08	3.0	40	118/74	0.08	1.4	17	80/50
7	0.04	1.7	50	102/70	0.04	1.4	35	102/68
8	0.07	2.4	37	142/80	0.08	1.6	21	110/66
9	0.08	1.6	20	142/80	0.12	1.7	13	110/66
10	0.05	2.2	46	130/100	0.05	1.3	27	140/100
11	0.08	2.8	37	130/100	0.08	1.8	24	140/100
12	0.10	3.0	31	104/70	0.11	2.5	24	110/68
13	0.04	2.3	54	104/70	0.04	1.6	42	110/68
14	0.08	2.5	33	130/80	0.08	1.7	23	124/72
15	0.07	2.0	31	130/80	0.07	1.4	20	124/72
16	0.06	1.7	30	138/76	0.05	0.9	18	130/90
17	0.08	2.8	37	140/86	0.07	1.4	20	130/80
18	0.06	2.0	32	118/80	0.07	1.5	22	120/65
19	0.06	1.8	31	118/80	0.06	1.2	20	120/65
20	0.12	3.5	31	190/110	0.11	2.0	18	140/80
21	0.08	3.8	50	190/110	0.09	2.3	27	140/80
22	0.08	2.4	32	130/84	0.07	1.4	20	115/80
23	0.10	2.9	31	130/84	0.09	1.6	18	115/80

Average change { Intraocular pressure = 13.2 mm. Hg ± 0.885 ; Systolic blood pressure = 14.4 mm. Hg ± 3.584

* *C*, facility of aqueous outflow, indicates cubic millimeters per minute per millimeter Hg pressure; *K*, total rate of flow in cubic millimeters per minute; IOP, millimeters Hg intraocular pressure, and B. P., blood pressure.

TABLE 2.—*Effect of Intramuscular Injection of 25 Mg. of Hexamethonium Chloride on Aqueous Humor Dynamics of Patient (Mrs. A) with Advanced Chronic Simple Glaucoma in Both Eyes Who Had Not Been Operated On and Had Had No Miotic Medication for Forty-Eight Hours Prior to Test* *

	O. D.			O. S.			
Time	*C*	*K*	IOP	*C*	*K*	IOP	B. P.
8:00 a. m.	0.08	2.4	32	0.10	2.9	31	130/84
8:15 a. m.	....	...	33	....	...	31	.....
8:20 a. m.	25 mg. hexamethonium injected subcutaneously						
9:00 a. m.	....	...	24	....	...	22	120/80
9:20 a. m.	0.07	1.4	20	0.09	1.6	18	115/80
10:30 a. m.	....	...	18	....	...	18	122/80
2:00 p. m.	....	...	25	....	...	25	.....
4:00 p. m.	....	...	29	....	...	31	132/80

* *C*, facility of aqueous outflow, indicates cubic millimeters per minute per millimeter Hg pressure; *K*, total rate of flow in cubic millimeters per minute; IOP, millimeters Hg intraocular pressure, and B. P., blood pressure.

extent in most of these patients, the average decrease in systolic blood pressure being 14.4 mm. Hg.

Table 2 illustrates the effect of hexamethonium on aqueous humor dynamics in chronic simple glaucoma. This patient (Mrs. A) had advanced glaucoma with marked field loss and cupping in both eyes, the intraocular pressure being adequately

controlled with miotics for the past year. When the drops were withheld for 48 hours, the intraocular pressure was 32 and 31 mm. Hg, respectively, in the right and left eyes. Hexamethonium chloride, 25 mg., injected intramuscularly, caused a drop of the intraocular pressure from 32 to 20 mm. and from 31 to 18 mm. Hg, respectively, in the right and left eyes. At the same time, the rate of flow of aqueous, *K*, decreased from 2.4 to 1.4 in the right eye and from 2.9 to 1.6 in the left eye. The facility of aqueous outflow remained approximately the same in the two eyes, and the systolic blood pressure dropped only 15 mm. Hg, from 130 to 115 mm. A few hours later, both the intraocular pressure and the blood pressure were back up to preinjection levels.

Table 3 shows the effect of hexamethonium when it was injected retrobulbarly. A dose of 2.5 mg. of hexamethonium chloride in 1.5 cc. of saline solution was injected retrobulbarly in 11 patients with chronic simple glaucoma. The intraocular pressure remained unchanged; there was no extraocular muscle paralysis, and the

TABLE 3.—*Effect of Retrobulbar Injection of 2.5 Mg. of Hexamethonium Chloride in 1.5 Cc. of Saline Solution on Intraocular Pressure of Patients with Chronic Simple Glaucoma Who Had Not Been Operated On and Had Had No Miotic Medication for Forty-Eight Hours Prior to Test* *

Eye No.	IOP Before Injection	IOP After Injection
1	41	40
2	40	38
3	27	31
4	42	40
5	35	36
6	28	32
7	28	30
8	53	51
9	51	54
10	33	34
11	34	32
12	44	44
13	34	26
14	34	29
15	32	34
Average	37.5	36.8

* IOP indicates millimeters Hg intraocular pressure.

visual acuity was not affected. The only noticeable change was a semidilatation of the pupils, which persisted for two to three hours. When more than 2.5 mg. of hexamethonium chloride was injected retrobulbarly, the patients showed some systemic effects, probably due to the absorption of the drug.

B. Thiopental Anesthesia.—Table 4 demonstrates the results obtained with intravenous injection of thiopental sodium in patients with chronic simple glaucoma. Preliminary work showed that 20 minutes was sufficient time to stabilize the patient with the anesthetic, and therefore the tonographic readings were done 20 minutes after the beginning of intravenous thiopental sodium anesthesia. The intraocular pressure fell markedly after the injection of the drug; 20 minutes after beginning the anesthesia (light surgical level) the average intraocular pressure dropped 19 mm. Hg. The tonographic measurements indicate that most of this drop in intraocular pressure was probably caused by a marked improvement of the facility of aqueous outflow, *C*. At the same time *K*, i. e., the rate of flow of aqueous, changed erratically; sometimes it increased and sometimes it decreased

TABLE 4.—*Effect of Thiopental Sodium Intravenous Anesthesia on Aqueous Humor Dynamics of Patients with Chronic Simple Glaucoma Who Had Not Been Operated On and Had No Miotic Medication for Forty-Eight Hours Prior to Test* *

	Before Anesthesia				20 Minutes After Start of Anesthesia					
Eye	*C*	*K*	IOP	B. P.	*C*	*K*	IOP	B. P.	Premedication	Supplementary Anesthesia Used
1	0.06	2.1	37	120/60	0.13	3.1	25	115/70	Scopolamine 0.5 mg.	Nitrous oxide
2	0.08	2.2	30	120/60	0.15	2.9	20	115/70	Scopolamine 0.5 mg.	Nitrous oxide
3	0.08	2.8	37	120/70	0.12	2.4	20	120/80	Scopolamine 0.6 mg.	Nitrous oxide
4	0.09	3.4	40	120/70	0.13	2.2	17	120/80	Scopolamine 0.6 mg.	Nitrous oxide
5	0.10	2.8	29	190/100	0.16	2.2	12	150/100	Atropine 0.5 mg.	Nitrous oxide
6	0.08	3.0	40	190/100	0.12	2.0	16	150/100	Atropine 0.5 mg.	Nitrous oxide
7	0.05	2.7	53	140/100	0.10	2.4	25	140/100	Scopolamine 0.5 mg.	Nitrous oxide
8	0.05	1.5	32	140/100	0.13	2.1	16	140/100	Scopolamine 0.5 mg.	Nitrous oxide
9	0.06	1.8	32	165/105	0.08	1.8	24	160/100	Scopolamine 1.0 mg., morphine 15 mg., & secobarbital 100 mg.	Nitrous oxide
10	0.05	1.9	41	120/80	0.15	2.6	17	100/70	Scopolamine 0.5 mg., meperidine 100 mg., & secobarbital 100 mg.	Nitrous oxide
11	0.04	2.0	57	120/80	0.12	2.7	24	100/70	Scopolamine 0.5 mg., meperidine 100 mg., & secobarbital 100 mg.	Nitrous oxide
12	0.06	2.2	40	170/80	0.05	1.3	27	160/90	Meperidine 50 mg. & atropine 0.5 mg.	Nitrous oxide
13	0.02	1.2	58	110/70	0.05	1.4	29	105/70	Scopolamine 0.5 mg.	None
14	0.08	2.8	37	110/70	0.10	1.5	15	105/70	Scopolamine 0.5 mg.	None
15	0.08	2.4	32	110/60	0.16	3.1	20	110/50	Atropine 0.5 mg.	None
16	0.06	2.2	40	110/60	0.11	2.5	24	110/50	Atropine 0.5 mg.	None
17	0.04	2.3	61	115/70	0.15	4.5	32	110/70	Atropine 0.5 mg.	None
18	0.04	2.5	66	115/70	0.18	6.1	37	110/70	Atropine 0.5 mg.	None
19	0.10	3.7	40	160/100	0.15	3.8	26	150/90	Atropine 0.5 mg.	None
20	0.12	3.6	32	160/100	0.18	3.6	20	150/90	Atropine 0.5 mg.	None

Average change { Intraocular pressure = 19.1 mm. Hg ± 1.62
Systolic blood pressure = 9.25 mm. Hg ± 2.70

* *C*, facility of aqueous outflow, indicates cubic millimeters per minute per millimeter Hg pressure; *K*, total rate of flow in cubic millimeters per minute; IOP, millimeters Hg intraocular pressure, and B. P., blood pressure.

TABLE 5.—*Effect of Thiopental Sodium Intravenous Anesthesia on Aqueous Humor Dynamics of Patient (Mr. B) with Chronic Simple Glaucoma Who Had Not Been Operated On and Had Had No Miotic Medication for Forty-Eight Hours Prior to Test* *

	O. D.			O. S.			
Time	*C*	*K*	IOP	*C*	*K*	IOP	B. P.
9:00 a. m.	0.05	1.9	41	0.04	2.0	57	120/80
9:05 a. m.	Scopolamine 0.5 mg., meperidine 100 mg., & secobarbital 100 mg. premedication						
10:00 a. m.	0.11	3.0	29	0.07	2.7	41	120/80
10:10 a. m.	....	...	28	....	...	42	110/70
10:15 a. m.	Thiopental I. V. anesthesia started						110/70
10:40 a. m.	0.15	2.6	17	0.12	2.7	24	100/70
10:50 a. m.	Patient waking up						
11:30 a. m.	Patient is awake						110/80
11:40 a. m.	....	...	42	....	...	60	.....

* *C*, facility of aqueous outflow, indicates cubic millimeters per minute per millimeter Hg pressure; *K*, total rate of flow in cubic millimeters per minute; IOP, millimeters Hg intraocular pressure, and B. P., blood pressure.

during the course of the anesthesia. The blood pressure varied only a small amount in most of these patients; the average drop in the systolic blood pressure was only 9 mm. Hg during the course of the anesthesia. Here, again, patients with approximately normal blood pressure and normal cardiovascular status were employed,

since it is well known that thiopental may lower the blood pressure of hypertensive patients. Nitrous oxide was used as a supplementary anesthetic in some of these patients (Table 4, Eyes 1-12), but the tonographic results were the same with and without this agent; therefore we can be justified in considering the group homogeneous.

The premedication of these patients is also indicated in Table 4. It was generally noted that atropine or scopolamine had no effect on the state of the intraocular pressure. However, morphine, secobarbital, or meperidine caused a decrease in the

TABLE 6.—*Effect of Thiopental Sodium Intravenous Anesthesia on Aqueous Humor Dynamics of a Patient (Mrs. C) with Chronic Simple Glaucoma Who Had Not Been Operated On and Had Had No Miotic Medication for Forty-Eight Hours Prior to Test* *

	O. D.			O. S.			
Time	*C*	*K*	IOP	*C*	*K*	IOP	B. P.
8:30 a. m.	0.06	2.4	32	0.06	2.2	40	110/60
8:50 a. m.	Atropine 0.5 mg. premedication given I. M.						
9:55 a. m.	....	...	33	....	...	40	.....
10:00 a. m.	Thiopental anesthesia (I. V.) started						100/60
10:20 a. m.	0.16	3.1	20	0.11	2.5	24	108/50
11:05 a. m.	Patient waking up						
11:15 a. m.	Patient fully awake						
11:20 a. m.	....	...	31	....	...	42	.....

* *C*, facility of aqueous outflow, indicates cubic millimeters per minute per millimeter Hg pressure; *K*, total rate of flow in cubic millimeters per minute; IOP, millimeters Hg intraocular pressure, and B. P., blood pressure.

TABLE 7.—*Effect of Sedation* * *on the Aqueous Humor Dynamics of Patients with Normal Eyes* †

	Before			After			General Effect of Sedation
Eye	*C*	*K*	IOP	*C*	*K*	IOP	
1.	0.22	3.1	16	0.20	2.8	16	Slight
2.	0.20	3.8	16	0.23	3.0	14	Slight
3.	0.12	1.5	14	0.12	1.4	13	Moderate
4.	0.20	3.0	17	0.17	2.6	15	Moderate
5.	0.20	3.1	17	0.18	2.8	17	Slight
6.	0.32	4.4	16	0.28	3.9	16	Slight
7.	0.16	2.2	16	0.17	1.9	12	Moderate
8.	0.15	1.9	14	0.15	1.7	12	Moderate
9.	0.20	3.0	17	0.19	3.0	19	Marked
10.	0.17	1.9	12	0.17	1.8	12	Slight
11.	0.19	2.3	13	0.18	2.1	12	Slight

* Secobarbital, 0.1 to 0.2 gm. given orally.

† *C*, facility of aqueous outflow, indicates cubic millimeters per minute per millimeter Hg pressure; *K*, total rate of flow in cubic millimeters per minute; IOP, millimeters Hg intraocular pressure, and B. P., blood pressure.

intraocular pressure even before thiopental sodium was administered to the patient. This can be seen more graphically in Table 5. This patient (Mr. B), who had well-established chronic simple glaucoma and whose tension was adequately controlled with pilocarpine drops, showed the following changes: Before the test started, the intraocular pressure (no drops for the past 48 hours) was 41 mm. Hg in the right eye and 57 mm. Hg in the left eye. Premedication consisted of 0.5 mg. of scopolamine hydrobromide, 100 mg. of meperidine hydrochloride, and 100 mg. of secobarbital given intramuscularly. One hour after this medication, the intraocular pressure in the right eye dropped from 41 to 29 mm. and in the left eye

from 57 to 41 mm. Hg; at the same time, the facility of aqueous outflow improved in both eyes, and the blood pressure remained unchanged. Thiopental sodium was then injected intravenously, and 25 minutes later the intraocular pressure in the right eye dropped to 17 mm. and in the left eye to 24 mm. Hg. The facility of aqueous outflow improved in both eyes, while the blood pressure dropped somewhat, the total change in the systolic pressure being only 20 mm. Hg. One hour after the administration of thiopental was discontinued the patient was fully awake and the ocular tension was back to pretest levels.

Table 6 illustrates the effect of thiopental anesthesia on another patient (Mrs. C) with chronic simple glaucoma. In this case atropine only (0.5 mg., given intramuscularly) was used as a preanesthetic medication. The intraocular pressure was not affected by the atropine, but thiopental sodium given intravenously caused a decrease in the intraocular pressure of both eyes (from 33 to 20 mm. O. D. and from 40 to 24 mm. O. S.) and a corresponding improvement of the facility of outflow, while the blood pressure stayed about constant. One hour later, when the patient was awake, the intraocular pressure was back up to the preanesthesia levels.

Table 7 shows the effect of premedication with barbiturate (secobarbital, 0.1 to 0.2 gm. given orally) on 11 normal eyes. The tonographic results indicate that the intraocular pressure, the facility of aqueous outflow, and the rate of flow were not influenced by the above medication. The systemic effect of the sedation was also noted and was described as slight, moderate, or marked, depending on the reactions of the patient.

COMMENT

A. Hexamethonium.—Previous reports on hexamethonium did not explain the mechanism of action of this drug on ocular tension. The present study, however, demonstrates that in eyes with chronic simple glaucoma the intraocular pressure decrease caused by hexamethonium is probably related to a simultaneous decrease in the rate of formation of aqueous. In this experiment the blood-pressure-lowering effect of hexamethonium was avoided by employing mainly normotensive patients and keeping them strictly horizontal to prevent orthostatic hypotension. It is known that a sudden, marked decrease in blood pressure is often reflected by a simultaneous decrease in the intraocular pressure; von Sallmann [22] has shown that the ratio of the change in the intraocular pressure to that in the blood pressure is usually 1 : 10. In the present investigation, however, the drop in the intraocular pressure has a ratio of about 1 : 1; thus it can be said with reasonable assurance that the fall in blood pressure was not sufficient to account for the decrease in the intraocular pressure.

At the same time, the facility of aqueous outflow remained constant during this experiment. Previous studies of Grant,|| Goldman,[25] Weekers,[26] and Kronfeld,[27] and reports from this department ¶ have indicated that constancy of the facility of aqueous outflow is one of the fundamental characteristics of chronic simple glaucoma. The first part of the present study is further evidence that the resistance to outflow in primary chronic simple glaucoma is a stable factor; at least it did not vary under the above-described experimental conditions.

|| References 23 and 24.

¶ References 28-30.

Injection of small amounts of hexamethonium retrobulbarly caused a pupillary dilatation but did not influence the intraocular pressure. This pupillary dilatation was probably due to an effect on the ciliary ganglion. Previous investigations of Carroll # and de Roetth have shown that when procaine was injected retrobulbarly it had an effect on all the surrounding nerve structures situated in the orbit, i. e., the ciliary ganglion, the nerves supplying the extraocular muscles, and the optic nerve itself. Hexamethonium, however, being a ganglionic blocking agent, has an effect on the ganglion only, and not on the nerve fibers; consequently, when injected retrobulbarly, it paralyzes the ciliary ganglion and not the adjacent nerve structures.

It should be pointed out that hexamethonium was employed as a research tool in this investigation to study the factors controlling ocular hydrodynamics in chronic simple glaucoma, and not as a therapeutic agent. Because of the transient pressure-lowering effect that it has on the eye and the marked, and often severe, systemic effects that it produces, hexamethonium is contraindicated in the treatment of glaucoma.

B. Thiopental Sodium Anesthesia.—The most significant result of this investigation was the fact that thiopental sodium anesthesia and/or premedication (morphine, meperidine, and secobarbital) produced a considerable drop in the intraocular pressure of eyes with chronic simple glaucoma, and that this decrease in ocular pressure was related to a decrease in the resistance to aqueous outflow. Since the above compounds are known central nervous system depressants, it may be assumed that their effect on aqueous humor dynamics was achieved by depressing some centers in the brain that have a controlling influence on the intraocular pressure by changing the resistance to outflow.

The factor of nervous control of aqueous humor dynamics is a controversial issue, which has been discussed and contemplated for many years. At present, there are two main schools of thought concerning the mechanism of primary glaucoma: The "neurovascular" * school believes that the tension of the eye is under neurovascular control, while the "mechanistic" school advocates that local mechanical factors, such as the resistance to the outflow of aqueous, control the intraocular pressure. There have been several attempts † in recent years to arrive at a compromise between these two schools of thought concerning the etiology of primary glaucoma. The present investigation is a further step in this direction. The above experiments indicate that in chronic simple glaucoma the central nervous system has some controlling influence on aqueous humor dynamics; however, it exerts its regulating effect by changing the resistance to the aqueous outflow, which is considered to be a local or mechanical factor in the anterior chamber angle. It was interesting to note that atropine or scopolamine premedication had no effect on the intraocular pressure. On the other hand, premedication with morphine, meperidine, and secobarbital (all of which are known central nervous system depressants) did cause a drop in ocular tension and an improvement in the facility of aqueous outflow.

A barbiturate, employed as a sedative before cataract operation, did not seem to affect the ocular hydrodynamics of these normal eyes. (These patients had cataract, but since their ocular pressure was normal on repeated occasions, the eyes

References 31 and 32.

* References 35-37.

† References 39 and 40.

were considered normal for the purpose of this study.) It should be pointed out that in these eyes the tension was already in the low or normal range before the barbiturate was administered, whereas in the glaucomatous eyes it was considerably elevated. Therefore, it is conceivable that the effect of the barbiturate on the aqueous humor dynamics of these "normal" eyes was in some manner eliminated or overshadowed by the low initial tensions of these eyes.

SUMMARY

Various factors regulating the intraocular pressure in chronic simple glaucoma were investigated with the tonographic method. Hexamethonium, a ganglionic blocking agent, caused a transient fall in the intraocular pressure, which was apparently due to a simultaneous decrease in the rate of flow of aqueous. The facility of aqueous outflow, however, and the blood pressure of these patients were not affected appreciably. Retrobulbarly injected hexamethonium caused only mydriasis and did not affect the other nerve elements in the orbit.

Intravenous thiopental sodium, and other central nervous system depressants employed as premedicating agents, caused a marked fall in the intraocular pressure in eyes with chronic simple glaucoma. This drop in intraocular pressure was apparently related to a simultaneous improvement in the facility of aqueous outflow and not to the rate of aqueous formation or to blood pressure changes.

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Dr. John H. Dunnington permitted the use of some of his private patients in this study.

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Diurnal Changes in Eosinophile Count

Comparison with Changes in Intraocular Pressure, Tonographic Values, and Aqueous Veins

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In the past, considerable emphasis has been placed on the conflict between the neurovascular and the mechanical theory of glaucoma. According to the first theory, primary glaucoma arises from a disturbance of the neurovascular system of the eye, whereas according to the mechanical theory it depends on alterations in the mechanics of aqueous humor flow. This conflict is particularly evident in congestive glaucoma (narrow-angle glaucoma), whereas in chronic simple glaucoma (wide-angle glaucoma) the two theories are more easily reconciled.

The detection of the aqueous veins (1941) and the introduction of tonography (1950), giving glaucoma research a new impetus, have led most authorities to agree that in chronic simple glaucoma an obstruction, type unknown, is present somewhere between the anterior chamber and the deep or superficial scleral veins. The immediate cause of this obstruction is most likely either a vasoconstriction or a sclerosis of the angle or adjacent structures. The ultimate cause is still a controversial subject. Sugar [1] summarized the various hypotheses as follows: (1) neurovascular stimuli: (*a*) autonomic, (*b*) psychic; (2) control center disturbance; (3) humoral.

Great emphasis was recently placed on the first point, neurovascular stimuli, by Thiel,[2] by Duke-Elder,[3] by Tassman,* and by others. Tassman said that any psychological stress could be a determining factor in the occurrence of glaucoma in the second eye of a patient suffering from the same disease in the fellow eye.

Next, the existence of a control center, most likely located in the hypothalamus or diencephalon, is strongly supported by Elwyn,† Schoenberg,[7] Loewenstein and Schoenberg,‡ Magitot,[10] Posner and Schlossman,[11] Weinstein,§ and von Sallmann and Lowenstein.[14] Schoenberg's theory is that psychic stimuli act on the control center, which, in turn, influences the hypophysis to produce the changes in intraocular pressure. Posner and Schlossman regard primary glaucoma as a single

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* Tassman, I. S., in discussion on paper by McDonald.[4]

† References 5 and 6.

‡ References 8 and 9.

§ References 12 and 13.

disease, of which the most important cause is an alteration of the central regulatory mechanism. The same authors consider the anatomic and physiochemical conditions of the eye as modifying and precipitating factors.

Finally, in favor of the humoral theory, evidence has been brought forward by Schmerl, Dietz, and Steinberg.‖ Having found that nicotine increases the response to the water-drinking test, Bietti and Cima [19] assumed that this drug might influence the hypophysis and performed additional experiments on animals after hypophysectomy. In these animals neither nicotine nor the water-drinking test increased intraocular tension, thus proving the important part played by the hypophysis in the regulation of intraocular pressure. Arén and Skanse [20] suggested two possible explanations of the increased intraocular pressure in acromegaly with glaucoma, namely, increased production of intraocular fluid and decreased facility of outflow. The latter hypothesis is the more probable, because their tonographic studies reveal a decreased facility of outflow. These authors concluded that increased production of the growth hormone by the hypophysis may tend to produce granulation and sclerosis of connective tissue. This sclerosing effect, if occurring in the chamber angle, may lead to a decrease of facility of outflow.

Stepanik [21] made a comparison of the diurnal variations of the circulating eosinophiles and intraocular pressure and concluded that a decrease in eosinophiles is often associated with an increase in the resistance to aqueous outflow and vice versa. He studied the diurnal changes of the tonographic readings and of the eosinophile counts in eight subjects, comprising 13 eyes—2 normal, the others affected by various types of glaucoma. In fact, five of these eyes had chronic simple glaucoma; one eye had chronic simple glaucoma but had had an iridencleisis; two eyes had aphakic glaucoma; three were suspected of having glaucoma, and two were normotensive. Stepanik followed the variations of the tonographic readings for one day or more at the following hours of the day: 6 and 9 a. m.; 12 noon, and 4, 7, and 10 p. m. Immediately after the determination of the tonographic values, the eosinophile count was performed on a sample of venous blood.

The variation in the circulating eosinophiles is mediated by the diencephalon-hypophysis system through secretion of corticosteroids by the adrenal cortex (Hume [22]; Porter [23]). Changes of circulating eosinophiles can occur only when the hypophysis-adrenal axis is intact, because corticotropin alone does not alter the eosinophile count (Hills, Forsham, and Finch [24]; Best, Kark, Muehrcke, and Samter [25]).

Because of the relationship which Stepanik believed to exist between intraocular pressure and eosinophile count, and, in turn, between the latter and the hypophysis, he inferred a direct influence of the hypophysis on the control of intraocular pressure.

OBJECTIVES OF THE PRESENT STUDY

Considering the interesting possibilities inherent in Stepanik's deductions, we decided not only to investigate more extensively the relationship between the number of eosinophiles and the intraocular pressure changes of normal and of glaucomatous eyes, but also to correlate other factors with the above changes. Among these factors, particular attention was given to the study of the aqueous veins, to find whether a correlation might exist between the diurnal variations of the appearance of the aqueous veins and the diurnal changes of tonographic values, and the eosinophile counts.

‖ References 15-18.

PERSONS STUDIED

Subjects studied here were limited to 21 sufferers from chronic simple glaucoma, representing 35 glaucomatous eyes, and 11 normal controls, 5 volunteer student nurses and 6 ward patients, representing 14 normal eyes.

Chronic simple glaucoma had been present for more than three years in 11, and for three years or less in 10, of our patients.

The diagnosis of chronic simple glaucoma was established on the basis of increased intraocular pressure, substantiated by a complete ophthalmological examination and, when necessary, by provocative tests. Eyes with absolute glaucoma were not included. None of the glaucomatous eyes had been subjected to surgery.

As far as ocular changes were concerned, very high intraocular pressure, deep cupping of the disc, and marked alterations of the peripheral and central visual fields were found in Patients 3, 4, 5, 7, 12, 13, 14, and 18. The others showed milder increase of ocular pressure, slight cupping of the disc, and moderate changes of the peripheral and central visual fields. Patients 3, 12, and 14 had absolute glaucoma in one eye; these eyes were excluded from our study. Patient 19 had a unilateral surgical anophthalmos, as a result of absolute glaucoma.

The patients suffering from chronic simple glaucoma had also the following diseases: arteriosclerosis and hypertensive vascular changes (Patients 1, 8, 9, 10, 15, 17, 19, and 20); inactive pulmonary tuberculosis (Patient 2); bronchial asthma (Patients 3 and 11); rheumatoid arthritis (Patients 4, 16, and 18); psychoneurosis and neurasthenia (Patients 5 and 7); rheumatoid spondylitis (Patient 6); hemorrhoids (Patient 12); prostatic carcinoma (Patient 13); chronic osteoarthritis (Patient 14), and hyperthyroidism (Patient 21).

The normal controls had a physical examination prior to testing, and only completely healthy persons were included. Of the ward patients, six with unilateral ocular trauma were selected after recovery from their eye lesion; only the uninjured eyes were subjected to measurements.

The ages of the glaucoma patients ranged from 43 to 76 years, with an average age of 58. The ages of the normal controls ranged from 18 to 48 years, with an average age of 26.

It would have been desirable to study normal subjects of ages comparable to those in the glaucoma group; such, however, were not available at the time of our investigation.

METHOD

Observation of the aqueous veins was performed before tonography or intraocular pressure measurements, to avoid changes in the aspect of the veins and in influx phenomena.

In 23 glaucomatous and 5 normal eyes, the diurnal variations of intraocular pressure were determined with the Schiøtz tonometer; tonographic studies with the Müller electronic tonometer without the recording unit were performed in 12 glaucomatous and 9 normal eyes. Both instruments were standardized. Use of miotics was discontinued for a period of 48 hours prior to and during the testing. Pressure readings were performed with the subject in the supine position, eyes in primary position, and clothing loosened around the neck. The lids were retracted manually in the Schiøtz group and by means of a nonmagnetic self-retaining speculum in the tonography group. Great care was taken to avoid eye massage during testing. All equipment was carefully cleaned and calibrated before each determination. The readings on the electronic tonometer were taken every 30 seconds for a period of four minutes by interpolating the figures between the extremities of oscillations caused by vascular and respiratory variations. The calculation of C (facility of aqueous outflow) and K (rate of aqueous flow) was by Grant's formula, as follows:

$$C = \frac{\Delta V}{(P_t\ av - P_0)\ t}$$

$$K = C \times P_0$$

The determinations were made every two hours from 8 a. m. to and including 8 p. m. Before each determination the cornea was examined for possible epithelial abrasions, and when any such was present, the testing was interrupted, to be completed after restoration of normalcy.

The eosinophile counts were performed immediately after the intraocular pressure measurements. Certified blood pipettes and a Levy corpuscle-counting chamber were used with Randolph diluting fluid for the eosinophile count.

Blood samples were obtained by finger-tip puncture, a separate digit being used for each determination. Although finger puncture did not allow absolute circulating eosinophile counts, it

did make possible successive determinations without perceptible alterations in number of circulating eosinophiles which occur with venipuncture methods (Naiden and Ross [26]). Rud [27] and Swanson and associates [28] assumed, on the basis of laboratory observations, that the eosinophile counts of venous and capillary blood are very similar. Best and associates state that the consistency of the counts obtained with venous blood is greater than that with capillary blood. On the average, eosinophile counts from free-flowing capillary blood would be expected to be comparable to, although slightly lower than, eosinophile counts from venous blood.

Meals were always taken at 8:30 a. m., 12:30 p. m., and 4:30 p. m., with a light repast at 9:30 p. m. The diurnal activity of all patients and normal subjects was regulated equally throughout the day.

The data were analyzed by calculation of linear correlation coefficients. The deviation of these coefficients from zero was tested for significance at the 5% level by use of an F test given by Goulden.[29] Fiducial limits were calculated by Fisher's [30] method for those coefficients which differed significantly from zero. Positive coefficients mean that eosinophile count and intraocular pressure increase or decrease together. Negative coefficients mean that the eosinophile count decreases as the intraocular pressure increases, and vice versa.

RESULTS

The intraocular pressure readings and the eosinophile counts performed immediately after are shown in Tables 1, 2, 3, and 4 for both normal and glaucomatous subjects. Values of correlation coefficients for these data are shown in Table 5.

TABLE 1.—*Diurnal Changes of the Eosinophile Count* * *in Normal Subjects*

	Time						
Subjects	8 a. m.	10 a. m.	12 N.	2 p. m.	4 p. m.	6 p. m.	8 p. m.
1	5	6	6	11	16	22	22
2	200	111	144	122	161	172	172
3	16	33	27	38	44	50	44
4	133	133	133	127	144	150	161
5	...	377	466	588	633	538	594
6	144	150	127	100	187	133	116
7	100	105	133	100	144	122	194
8	238	211	294	272	278	238	...
9	138	88	122	88	155	127	83
10	144	83	155	127	122	172	150
11	205	194	150	144	161	188	200

* Per cubic millimeter.

TABLE 2.—*Diurnal Changes of Intraocular Pressure* * *in Normal Subjects*

	Time						
Subjects	8 a. m.	10 a. m.	12 N.	2 p. m.	4 p. m.	6 p. m.	8 p. m.
1 OD	15.1	17.1	10.1	14.4	14.4	14.4	13.1
2 OD	24.6	23.0	19.9	24.6	2.30	23.0	24.6
3 OD	23.0	21.5	24.6	21.5	17.1	21.5	19.9
4 OS	23.0	18.5	18.5	18.5	17.1	17.1	15.7
5 OD	26.5	24.6	21.5	26.5	21.5	21.5	23.0
6 OS	25.0	25.8	23.8	23.0	21.4	23.0	23.0
7 OD	22.12	25.7	23.8	21.8	22.7	22.7	22.7
OS	22.7	26.4	24.2	25.7	26.0	20.0	25.0
8 OS	21.8	20.4	21.0	20.4	21.0	20.1	....
9 OS	17.2	17.2	17.2	16.9	16.9	16.3	15.8
10 OD	19.4	19.1	19.1	21.1	20.7	19.1	21.8
OS	26.4	22.7	22.1	19.4	22.1	22.1	24.6
11 OD	24.4	26.2	23.4	25.7	25.4	25.7	25.4
OS	25.4	25.4	21.8	21.8	21.8	25.0	23.4

* In millimeters of mercury.

TABLE 3.—*Diurnal Changes of the Eosinophile Count* * *in Chronic Simple Glaucoma*

	Time						
Subjects	8 a. m.	10 a. m.	12 N.	2 p. m.	4 p. m.	6 p. m.	8 p. m.
1	78	112	89	87	61	73	80
2	36	33	27	48	75	39	44
3	350	477	500	444	138	295	361
4	206	144	200	252	305	172	94
5	50	27	66	88	61	50	116
6	91	94	75	73	61	77	66
7	44	44	50	61	61	111	66
8	50	38	38	34	61	38	34
9	100	105	66	94	133	100	144
10	11	27	42	105	66	66	77
11	205	283	300	300	261	344	205
12	50	111	55	61	66	77	83
13	177	196	211	163	189	233	261
14	150	...	155	150	150	205	177
15	83	83	88	105	111	111	111
16	44	55	38	61	66	55	66
17	144	133	150	144	166	187	166
18	405	344	394	461	373	405	344
19	83	38	44	116	127	72	105
20	133	211	216	288	194	266	227
21	94	116	83	105	66	72	...

* Per cubic millimeter.

TABLE 4.—*Diurnal Changes of the Intraocular Pressure* * *in Chronic Simple Glaucoma*

		Time						
Subjects		8 a. m.	10 a. m.	12 N.	2 p. m.	4 p. m.	6 p. m.	8 p. m.
1	OD	30.3	26.5	30.3	40.0	32.3	32.3	28.3
	OS	30.3	30.3	37.3	49.5	34.7	32.3	24.6
2	OD	40.0	40.0	30.3	40.0	37.2	24.6	30.3
	OS	42.9	43.5	32.3	34.7	34.7	26.5	26.5
3	OS	37.2	30.3	28.5	23.0	25.6	24.6	24.6
4	OD	55.1	51.6	58.9	42.5	42.9	63.2	72.1
	OS	62.9	48.3	58.9	42.5	29.0	58.9	72.1
5	OD	58.9	55.1	51.6	45.6	55.1	45.6	48.3
	OS	39.9	46.0	42.5	42.5	37.6	37.6	37.6
6	OD	37.2	36.7	34.7	34.7	30.3	30.3	30.3
	OS	30.3	29.1	26.5	26.5	26.5	24.6	24.6
7	OD	48.3	51.6	45.3	45.3	42.5	39.9	45.6
8	OD	30.3	30.3	28.3	28.3	24.6	28.3	26.4
	OS	32.3	32.3	32.3	32.3	30.3	32.3	30.3
9	OD	37.2	30.3	24.6	23.0	28.3	30.3	32.7
10	OS	32.7	30.3	30.3	28.3	26.5	28.3	26.5
11	OD	37.2	32.3	32.3	32.3	28.3	30.3	30.3
	OS	34.7	30.3	30.3	34.7	30.3	28.3	26.5
12	OS	46.0	46.0	40.0	42.9	42.9	37.2	37.2
13	OD	58.9	58.9	62.9	55.1	55.1	42.5	37.5
	OS	46.0	42.9	46.0	37.2	34.7	24.6	24.6
14	OD	58.9	67.4	72.1	62.9	72.1	72.1	72.1
	OS	45.3	37.2	37.2	30.3	32.7	30.3	30.3
15	OS	34.7	34.7	32.3	32.0	22.4	23.0	22.1
16	OD	30.3	25.8	22.7	23.0	20.2	21.5	21.5
	OS	32.3	29.5	23.3	24.6	21.8	21.5	19.9
17	OD	34.7	34.7	34.7	34.6	23.2	27.5	27.2
	OS	34.7	34.7	33.7	35.1	30.3	26.5	26.5
18	OD	35.7	30.2	34.7	32.3	31.9	27.9	20.5
	OS	34.7	30.7	37.7	37.2	37.2	27.9	21.1
19	OD	24.2	24.9	25.7	23.0	23.6	23.0	21.8
20	OD	30.4	26.5	30.3	32.2	30.3	29.1	28.3
	OS	35.7	31.1	30.3	30.4	28.5	29.3	28.3
21	OD	31.5	28.7	28.5	27.4	27.4	23.1	....
	OS	32.0	24.6	31.1	26.5	24.6	22.4	....

* In millimeters of mercury.

TABLE 5.—*Correlation Between Eosinophile Count and Intraocular Pressure*

Normal Subjects		Glaucomatous Patients			
Subject and Eye	r	Subject and Eye	r	Fiducial Limits	Comment
		Group I: r Significantly Different from Zero			
		17 OS	−0.906*	−0.481 to −0.976	
		15 OS	−0.902*	−0.464 to −0.986	E.C. and I.O.P. correlate with aqueous vein appearance
		17 OD	−0.829	−0.202 to −0.974	
		7 OD	−0.819	−0.172 to −0.972	
		10 OD	−0.799	−0.091 to −0.967	
		13 OD	−0.767	−0.029 to −0.964	
11 OS	+0.810				
		Group II: r Not Significantly Different from Zero			
		20 OS	−0.747		
		19 OD	−0.713		(E.C. and I.O.P. correlate with aqueous vein appearance)
		13 OS	−0.687		
		4 OS	−0.678		
		4 OD	−0.662		(E.C. and I.O.P. correlate with aqueous vein appearance)
4 OS	−0.657				
3 OD	−0.646	16 OD	−0.554		
		5 OD	−0.525		(E.C. and I.O.P. correlate with aqueous vein appearance)
3 OS	−0.511				
		16 OS	−0.500		
		14 OS	−0.472		
		5 OS	−0.432		(E.C. and I.O.P. correlate with aqueous vein appearance)
		8 OD	−0.388		
		8 OS	−0.385		
		11 OD	−0.359		
		1 OD	−0.312		
5 OD	−0.296				
7 OD	−0.084	2 OS	−0.127		
		20 OD	−0.054		
		11 OS	−0.038		
1 OD	−0.012				
10 OD	−0.006				
		12 OS	+0.021		
		1 OS	+0.031		
		6 OS	+0.111		
7 OS	+0.123				
10 OS	+0.160				
		3 OS	+0.161		
8 OS	+0.190	21 OS	+0.164		
		2 OD	+0.209		
11 OD	+0.219				
2 OD	+0.260				
		18 OD	+0.265		
9 OS	+0.310	6 OD	+0.342		
		9 OD	+0.419		
		14 OD	+0.468		
		21 OD	+0.511		
		18 OS	+0.556		

* r Significant at 1% level; r is the linear coefficient of correlation.

TABLE 6.—*Diurnal Changes in Tonographic Values in Normal Subjects*

Subjects		Time						
		8 a. m.	10 a. m.	12 N.	2 p. m.	4 p. m.	6 p. m.	8 p. m.
6 OD	T*	25.00	23.80	23.80	23.08	21.46	23.08	23.08
	C	0.28	0.25	0.25	0.25	0.27	0.40	0.24
	K	5.96	5.16	5.16	4.57	4.98	6.51	4.48
7 OD	T	22.12	25.74	23.80	21.80	22.74	22.74	22.74
	C	0.30	0.23	0.21	0.27	0.24	0.29	0.31
	K	5.66	5.01	4.27	4.81	4.52	5.47	5.84
OS	T	22.74	26.42	24.20	25.74	26.06	20.06	25.00
	C	0.35	0.30	0.25	0.35	0.15	0.28	0.29
	K	6.80	4.68	5.25	7.63	3.34	4.94	4.17
8 OS	T	21.80	20.44	21.00	20.44	21.00	20.10	....
	C	0.21	0.24	0.22	0.21	0.25	0.34	....
	K	3.89	4.09	3.90	3.66	4.44	5.85	....
9 OS	T	17.22	17.22	17.22	16.90	16.90	15.38	15.86
	C	0.35	0.36	0.35	0.40	0.42	0.51	0.58
	K	5.27	5.42	5.27	5.72	6.02	7.35	7.44
10 OD	T	19.46	19.14	19.14	21.12	20.78	19.14	21.80
	C	0.20	0.21	0.25	0.29	0.33	0.31	0.34
	K	3.32	3.46	4.12	5.21	5.82	5.15	6.31
OS	T	26.42	22.76	22.12	19.46	22.12	22.12	24.60
	C	0.40	0.32	0.35	0.28	0.36	0.37	0.33
	K	4.74	6.21	6.59	4.64	6.78	6.97	6.86
11 OD	T	24.40	26.20	22.40	25.74	25.40	25.74	25.40
	C	0.35	0.47	0.52	0.54	0.42	0.47	0.39
	K	7.28	10.56	10.41	11.85	9.07	9.92	8.82
OS	T	25.40	25.40	21.80	21.80	21.80	25.08	23.40
	C	0.53	0.45	0.41	0.39	0.35	0.41	0.35
	K	11.45	9.72	7.61	7.24	6.49	8.79	7.61

* Millimeters of mercury.

TABLE 7.—*Diurnal Changes in Tonographic Values in Chronic Simple Glaucoma*

Subjects		Time						
		8 a. m.	10 a. m.	12 N.	2 p. m.	4 p. m.	6 p. m.	8 p. m.
15 OS	T*	34.70	34.70	32.20	32.00	22.44	23.08	22.12
	C	0.12	0.15	0.16	0.25	0.25	0.28	0.25
	K	3.60	4.50	4.46	6.83	4.75	5.53	4.75
16 OD	T	30.30	25.82	22.70	23.00	20.22	21.50	21.50
	C	0.20	0.19	0.20	0.25	0.20	0.22	0.22
	K	5.20	4.18	3.85	4.80	3.45	4.01	4.01
OS	T	32.30	29.50	23.32	24.00	21.80	21.50	19.00
	C	0.13	0.13	0.19	0.22	0.22	0.23	0.24
	K	3.53	3.27	3.66	4.62	4.60	4.19	4.08
17 OD	T	34.70	34.70	34.70	34.60	33.26	27.56	27.22
	C	0.29	0.26	0.23	0.18	0.30	0.26	0.26
	K	8.70	7.80	6.90	5.32	8.02	6.12	6.08
OS	T	34.70	34.70	33.74	35.16	30.30	26.50	26.50
	C	0.30	0.28	0.24	0.22	0.30	0.27	0.29
	K	8.70	8.40	6.82	6.56	7.80	5.67	6.09
18 OD	T	25.70	26.20	24.70	22.30	21.90	27.94	20.54
	C	0.05	0.10	0.10	0.10	0.10	0.10	0.13
	K	1.54	3.15	3.00	2.79	2.75	2.36	2.27
OS	T	34.70	30.70	37.76	37.30	37.20	27.94	20.54
	C	0.04	0.04	0.14	0.12	0.10	0.10	0.13
	K	1.20	1.06	4.56	3.87	3.23	2.36	2.27
19 OD	T	24.28	24.98	25.74	23.00	23.64	23.00	21.80
	C	0.18	0.00	0.14	0.20	0.21	0.15	0.25
	K	3.72	1.91	3.07	3.91	4.23	2.93	4.56
20 OD	T	30.46	26.50	30.30	33.26	30.30	29.10	28.30
	C	0.17	0.15	0.18	0.18	0.21	0.28	0.26
	K	4.71	3.38	4.08	4.60	5.46	6.97	6.29
OS	T	35.70	31.10	30.30	30.46	28.30	29.30	28.30
	C	0.25	0.31	0.29	0.27	0.30	0.36	0.35
	K	7.78	6.60	6.54	7.11	7.26	9.58	8.47
21 OD	T	31.52	28.70	26.50	27.40	27.40	21.18	.....
	C	0.30	0.15	0.16	0.24	0.20	0.14	.....
	K	8.07	3.67	3.38	5.57	4.64	2.52	.....
OS	T	32.60	24.60	31.10	26.50	24.60	22.40	.....
	C	0.24	0.13	0.16	0.22	0.17	0.14	.....
	K	6.55	2.73	4.27	4.96	3.57	2.66	.....

* Millimeters of mercury.

TABLE 8.—*Correlation Between Eosinophile Count and Production of Aqueous Humor*

Normal Subjects			Glaucomatous Patients			
Subjects and Eye	r	Difference from Zero	Subjects and Eye	r	Difference from Zero	Fiducial Limits
11 OD	−0.69	Not significant				
			17 OS	−0.67	Not significant	
7 OS	−0.64	Not significant				
			16 OD	−0.29	Not significant	
8 OS	−0.27	Not significant				
			17 OD	−0.26	Not significant	
6 OS	−0.19	Not significant				
9 OS	−0.17	Not significant				
			18 OD	−0.13	Not significant	
			21 OS	+0.17	Not significant	
10 OS	+0.22	Not significant				
7 OD	+0.23	Not significant				
10 OD	+0.31	Not significant				
			20 OS	+0.36	Not significant	
			20 OD	+0.44	Not significant	
			18 OS	+0.46	Not significant	
			15 OS	+0.57	Not significant	
11 OS	+0.64	Not significant				
			16 OS	+0.65	Not significant	
			19 OD	+0.87	Significant	+0.346 to +0.981

TABLE 9.—*Correlation Between Eosinophile Count and Facility of Outflow*

Normal Subjects				Glaucomatous Patients			
Subject and Eye	r	Difference from Zero	Fiducial Limits	Subject and Eye	r	Difference from Zero	Fiducial Limits
11 OD	−0.79	Significant	−0.004 to −0.908	18 OD	−0.37	Not significant	
8 OS	−0.29	Not significant					
7 OS	−0.24	Not significant					
9 OS	−0.10	Not significant					
6 OS	−0.11	Not significant					
				21 OS	+0.15	Not significant	
				OD	+0.18	Not significant	
				18 OS	+0.20	Not significant	
				17 OS	+0.20	Not significant	
7 OD	+0.24	Not significant					
				OD	+0.27	Not significant	
10 OD	+0.37	Not significant					
				16 OD	+0.40	Not significant	
OS	+0.44	Not significant					
11 OS	+0.46	Not significant					
				20 OD	+0.50	Not significant	
				16 OS	+0.58	Not significant	
				20 OS	+0.73	Not significant	
				19 OD	+0.87	Significant	+0.339 to +0.981
				15 OS	+0.97*	Significant	+0.823 to +0.996

* Significant at 1% level.

TABLE 10.—*Stepanik's Data, Statistically Evaluated*

Correlation Between Eosinophile Count and Intraocular Pressure

Normal Subjects			Glaucomatous Patients			
Subject and Eye		r	Subject and Eye		r	Fiducial Limits
Group I: r Significantly Different from Zero						
			KE	OD	−0.995*	−0.776 to −1.000
				OS	−0.907*	−0.486 to −0.986 (iridencleisis)
			IA	OD	−0.902	−0.102 to −0.994
			HM	OD	−0.873*	−0.497 to −0.973
				OS	−0.692	−0.054 to −0.929
Group II: r Not Significantly Different from Zero						
			BR	OS	−0.387	
MJ	OD	−0.492				
MW	OS	+0.445				

Correlation Between Eosinophile Count and Facility of Outflow

Subject and Eye		r	Difference from Zero	Subject and Eye		r	Difference from Zero
				KE	OS	−0.394	Not significant
				BR	OS	+0.379	Not significant
				HM	OS	+0.396	Not significant
					OD	+0.408	Not significant
MS	OD	+0.465	Not significant				
WW	OS	+0.484	Not significant	IA	OD	+0.509	Not significant
				KE	OD	+0.889	Not significant

Correlation Between Eosinophile Count and Production of Aqueous Humor

Subject and Eye		r	Difference from Zero	Subject and Eye		r	Difference from Zero
				KE	OD	−0.144	Not significant
				HM	OD	−0.183	Not significant
				BR	OS	−0.275	Not significant
				HM	OS	−0.332	Not significant
				KE	OS	−0.502	Not significant
				IA	OD	−0.686	Not significant
MJ	OD	+0.306	Not significant				
WW	OD	+0.532	Not significant				

*Significant at 1% level.

The values of production of aqueous humor and of facility of outflow are given in Tables 6 and 7 for both normal and glaucomatous eyes. Values of the correlation coefficients for these data with the simultaneous eosinophile count are shown in Tables 8 and 9.

Results of the statistical analysis of Stepanik's data are given in Table 10.

None of our normal subjects showed a relation between intraocular pressure and the appearance of the aqueous veins, or between the eosinophile count and the appearance of the aqueous veins. Among those glaucomatous patients in whom it was possible to study the appearance of the aqueous veins, only five showed a relation between these vessels, on the one hand, and the ocular tension or the eosinophile count, on the other. In Patient 4, the aqueous vein was pink at 2 and 4 p. m., when the intraocular pressure was low and the eosinophile count high; at all other hours of observation the aqueous vein was red, with high ocular tension and low eosinophile count. In Patient 5, a red aqueous vein and a blood influx phenomenon corresponded always with high intraocular pressure and low values of eosinophiles. Patients 15 and 19 had, in the morning, high ocular tension, low eosinophile count, and pink aqueous veins, whereas in the afternoon the tension became low, the eosinophile count high, and the aqueous veins clear. Patient 21 showed a similar relation between eye pressure and appearance of the aqueous veins; however, the eosinophile count was greater in the morning than in the evening.

COMMENT

Intraocular Pressure and Eosinophile Count.—When all eosinophile counts were plotted graphically against all intraocular pressures, no apparent relation was seen for either normal or glaucomatous eyes. However, when such plots were made for each individual eye, a definite linear relation was found in some cases, whereas no relation was seen in others. Calculation and testing of coefficients of correlation (r) of eosinophile count and intraocular pressure for each eye showed that the glaucomatous eyes can be divided into two groups: (I) those with r significantly

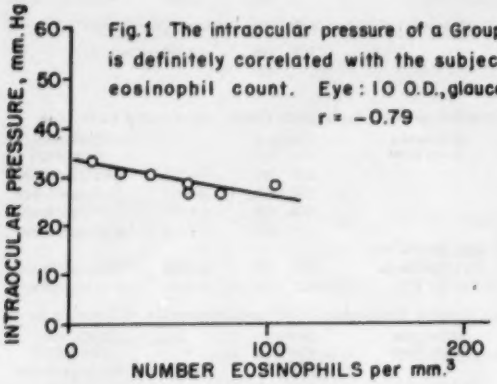

Fig. 1 The intraocular pressure of a Group I eye is definitely correlated with the subject's eosinophil count. Eye: 10 O.D., glaucomatous r = −0.79

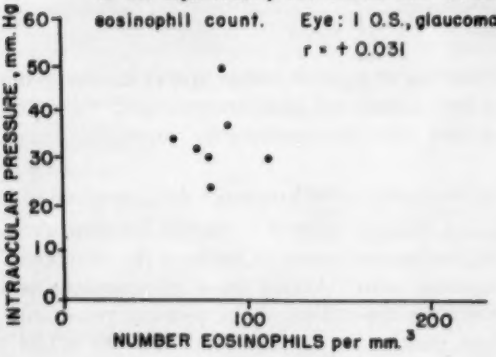

Fig. 2 The intraocular pressure of a Group II eye is not significantly correlated with the subject's eosinophil count. Eye: 1 O.S., glaucomatous r = + 0.031

different from zero and negative, and (II) those with coefficient not significantly different from zero (Figs. 1 and 2).

Five glaucomatous subjects belonged to Group I: Patients 7, 10, 13, 15, and 17. For Patient 13, r, O. D. was significant, r O. S. was not significant, but rather high. Additional measurements on the left eye of Patient 13 probably would move this eye up to Group I. In addition, there were at least seven other glaucomatous eyes (Patient 4 O. D. and O. S., Patient 5 O. D., Patient 16 O. D. and O. S., Patient 19 O. D., and Patient 20 O. S.) which, very possibly, might be classed as Group I if additional data were taken. For the other 21 glaucomatous eyes, the r ranged from

—0.472 to +0.556, not differing from zero enough to be ascribed to anything other than chance, and with about as many coefficients negative as positive. No relation existed between age and grouping.

Only one normal subject (Patient 11 O. S., an 18-year-old woman), had a coefficient significantly different from zero. We show this subject in Group I, but it should be pointed out that the coefficient for this eye was positive (+0.810); the coefficient for the right eye was —0.219. We do not know why the left eye was exceptional. For the other normal eyes, r ranged between —0.657 and +0.310.

Analysis of the data presented by Stepanik showed that all of his patients with definite, uncomplicated chronic simple glaucoma showed coefficients that were negative and significantly different from zero. The two normal eyes showed no significant correlation.

Other Tonographic Values and Eosinophile Count.—Of the glaucomatous eyes, none of Stepanik's and only one of ours (Patient 19 O. D.) had a significantly high correlation (+0.87) between rate of production (K) of aqueous humor and eosinophile count. For the other glaucomatous eyes, r ranged from —0.69 to +0.65.

No relation between rate of production and eosinophile count could be demonstrated in any of the normal eyes, either ours or Stepanik's. The r values ranged from —0.69 to +0.64.

Among the glaucomatous eyes, none of Stepanik's and only two of ours (Patient 19 O. D. and Patient 15 O. S.) had a significantly high correlation between facility of outflow (C) and eosinophile count. It is interesting that only 2 of the coefficients were negative; 16 were positive.

Of the subjects with normal eyes, only one (Patient 11 O. D.) had a definite correlation between facility of outflow and eosinophile count. None of the others, including Stepanik's, showed a significant value for r. There were six positive r's and five negative r's.

Aqueous Veins and Eosinophile Count.—Only in a few glaucomatous eyes was it possible to see a correlation between the appearance of the aqueous veins and the eosinophile count. It could be possible that in some of our subjects the changes in width, flow, and content of aqueous veins were very small and therefore escaped our observation. In any case, in Patients 15 and 19, when the intraocular pressure was high and the eosinophile count low, the aqueous veins were full of blood, whereas with the ocular tension low and the number of circulating eosinophiles high the content of the aqueous veins became very clear. It is interesting that in Patient 15 the correlation coefficient was very high, —0.902, and significantly different from zero; Patient 19 also had a very high correlation, —0.713, although it was not significantly different from zero. The other patients, too, when changes in the appearance of the aqueous veins were seen, had a coefficient that was high, although not significantly different from zero.

In the normal subjects, no correlation was found between the diurnal variations of intraocular pressure and circulating eosinophiles, on the one hand, and the appearance of the aqueous veins, on the other.

CONCLUSIONS

All our data show that from the patients affected with chronic simple glaucoma, approximately one-fourth (Group I) can be separated. These cases were characterized by the high correlation between the intraocular pressure and the number of circulating eosinophiles per cubic millimeter throughout their diurnal variations.

However, these subjects were not different from the other glaucomatous patients, in duration of the disease, magnitude of tonographic values, pathological modifications of the ocular tissues, or visual field changes.

If it is assumed that the variations of the circulating eosinophiles are regulated by the diencephalon-hypophysis region through the adrenal cortex, one might expect, as Stepanik suggested, that the same center would regulate the intraocular tension in these particular cases.

However, we do not concur with Stepanik concerning the mechanism of action of this center. Stepanik wrote:

> As, furthermore, it has been detected that in glaucomatous eyes changes of the resistance to the drainage of aqueous humor went in the same direction as changes in intraocular pressure, it is likely that primarily the resistance, and secondarily the pressure, is influenced by this central regulating mechanism.[21]

However, the statistical analysis of the data did not demonstrate any relation between the diurnal variations of the facility of outflow and those of the eosinophile count except in 2 eyes out of a total of 18, including Stepanik's. At the present time, therefore, we do not know of any mechanism that would account for the correlations found. We can exclude as a mechanism the regulation by the hypophysis and the diencephalon of the intraocular tension through the secretion of corticotropin, because it has been demonstrated by Blake and co-workers [31] and by Tillet [32] that this hormone does not influence the ocular pressure, although in their patients the eosinopenic response was good.

It is interesting that the relation between eosinophile count and intraocular pressure seems present only in some of the glaucomatous patients and in none of the normal subjects.

It would be of great interest to ascertain whether the relation between eosinophile count and intraocular pressure proves to be constant over a period of time in Group I patients. If so, it might indicate that these patients represent a special type of chronic simple glaucoma, characterized by an inverse correlation between eosinophile count and intraocular pressure, in addition to the well-known ocular signs and symptoms.

In 1954 Boles-Carenini,[33] working in this department, found that in glaucomatous patients there are two types of relations between intraocular pressure and systemic venous pressure. It might also be interesting to find out whether either of his groups coincides with our Group I. Such a coincidence would confirm the existence of a special type of chronic simple glaucoma.

SUMMARY

Our objectives in this study were to evaluate Stepanik's hypothesis of a hypophyseal regulation of intraocular pressure of glaucomatous eyes, based on his findings of an inverse relation between eye pressure and eosinophile count; to compare, as did Stepanik, diurnal variations of eosinophile count with those of aqueous-humor production and facility of outflow, and to study the appearance of the aqueous veins.

Statistical analysis of our data, obtained on 35 glaucomatous and 14 normal eyes, showed that our subjects fall into two groups: (I) eyes with a significantly high and negative correlation between eosinophile count and intraocular pressure, comprising five of the glaucomatous patients and none of the normal subjects, and (II) eyes with a correlation coefficient not significantly different from zero.

None of the normal eyes showed a relation between appearance of the aqueous veins, on the one hand, and eosinophile count and intraocular pressure, on the other; however, such a relation was found in 6 of the 30 glaucomatous eyes in which the aqueous veins were studied.

It is possible that the diencephalon-hypophysis region influences the intraocular pressure in certain cases of chronic simple glaucoma (our Group I). From our data it is not possible to explain what the mechanism of this influence might be. We can exclude the assumption that corticotropin influences the ocular tension directly and the possibility that the facility of outflow of aqueous humor is primarily affected by the diencephalon-hypophyseal region.

The possibility of the existence of a special type of chronic simple glaucoma is discussed.

Dr. K. W. Ascher gave helpful advice in this study.

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The Effect of Homatropine on the Accommodation-Convergence Association

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INTRODUCTION

The accommodative convergence is defined as that portion of the total convergence of the eyes that is initiated by the stimulus to accommodation by virtue of the accommodation-convergence synkinesis. The existence of this part of the convergence can be easily demonstrated by the change in the lateral heterophoria that occurs when ophthalmic spheres are placed before the eyes to alter the stimulus to accommodation. The initiation of this involuntary psycho-optical association is assumed by Bielschowsky [1] to be in the prestriate area of the occipital cortex.

There are three points of view relating to the origin and to the stability of the accommodation-convergence association.

The first of these points of view is that the association is a labile and flexible one and is entirely learned. According to this point of view, the association probably develops in the early years of the life of the individual because of the constant and repeated simultaneous use of functionally related degrees of accommodation and of convergence. Thus, the two functions tend to become associated as a conditioned reflex, so that the stimulation of one will result in a response of the other, provided that the second is free to act (Tait [2]). Duke-Elder [3] also expressed the opinion that the relationship between the two functions is very elastic. Accommodation can, therefore, be changed to a certain extent without changing convergence, and vice versa. Donders [4] similarly believed that there is a degree of independence in the relationship and described the amount of mutual freedom as "relative." His pupil Landolt [5] also wrote that the relationship between accommodation and convergence is not absolute, but, on the other hand, that there are limits to their independence.

The second point of view is that the association of the two functions is innate and generally invariable, its magnitude tending to remain constant throughout the lifetime of the individual. This hypothesis implies some type of fixed neural

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pathways. It was Maddox' * belief that the efforts of convergence and accommodation are intimately intersusceptible, so that the slightest impulse to either affects the other, although the difference would not need to be equal in amount. He found in the typical emmetrope that for each diopter of accommodation there was an accompanying 0.75 meter angle (about 4.7 △) of associated convergence.

In their haploscopic studies, Ames and Gliddon [6] found the relationship between accommodation and convergence to be definite and fixed. They stated that the convergence is always changed by a change in the accommodative stimulus and, conversely, that the accommodative state is changed by a change in the convergence. They denied that either relative accommodation or relative convergence exists.

Another proponent of this theory of a fixed accommodation-convergence association is Morgan.[7] In his investigations with the haploscope [8] he found that it was impossible to change accommodation by any amount without at the same time changing convergence. If the actual change in accommodation is considered, the change in convergence has a linear quantitative relationship to the change in accommodation. This linear relationship between accommodation and convergence was also found by Ogle, Mussey, and Prangen [9] and by Ogle and Prangen [10] throughout the range of response to accommodation. They used the fixation disparity technique; thus, fusion and binocular coordination were maintained throughout the tests. To Morgan and Peters [11] the accommodative convergence seemed to be connected with accommodation by some central association.

Finally, the third point of view combines the two points of view just described: that there is a certain innateness in the association, but at the same time it may be modified through the experience and the stresses encountered during the lifetime of the individual. This point of view is well expressed by Charnwood,[12] who stated that there is a tightly linked inborn accommodation-convergence relationship, which is adequate for the needs of animals not possessing a high visual acuity, but this is not good enough for man, with his high visual acuity and need of sharp binocular vision at near distances. In order to adjust this association to the varying requirements of the individual, there has been built on this unconditioned "occipital" reflex a conditioned "harmonic" reflex. The latter must be, and must remain, a conditioned reflex, because its function is to give the flexibility necessitated by individual variation to an inborn reflex. This harmonic reflex is lacking in infancy and is normally formed and consolidated in childhood by the reward of clearer vision which follows regularly some random changes of innervation for accommodation. As with other conditioned reflexes, it is in a state of vigorous flux in childhood and becomes progressively less fluid with increasing age. At what age this reflex may become fixed and unalterable is uncertain, but it probably retains some flexibility as far as the presbyopic age, and enables the individual to adapt to the changing conditions brought about by the failure of accommodation. It is only with this conditioned reflex association that the orthoptist can work, and it is the steady approximation of conditioned reflexes to the fixity of the inborn reflex which limits the age at which orthoptics can be effectual. Finally, Charnwood concluded that in normal subjects the occipital (unconditioned) and harmonic (conditioned) accommodative reflexes behave as one unconditioned reflex, despite the fact that the latter is a conditioned reflex which retains some flexibility into, at least, late adult life.

To what extent the inverse relationship—convergence-accommodation association—also exists is uncertain, because the difficulties of measurement have prevented

* Maddox, E. C., cited by Morgan.[7]

definitive results. The retinal accommodative reflex to preserve clear vision is so strong that it masks the effect of a convergent-accommodative synkinesis. Evidence from a recent experiment by Morgan [8] tends to show, however, a convergence-accommodation association.

From a practical point of view the magnitude of the accommodation-convergence association is a factor to be taken into consideration in the prescribing of ophthalmic lenses. In a patient with some degree of convergence difficulty, one must be more careful in prescribing additional plus corrections if the ratio of accommodation-convergence to accommodation is large than if it is small.

In order to learn more about this accommodation-convergence function, one must search for means by which the magnitude of the association can be altered. The extent to which certain drugs which cause a paresis of the ciliary body and iris sphincter, or drugs which cause spasm of these muscles, affect the magnitude of the association of accommodation and convergence must be further investigated.

In the present study the ratio of the change in convergence caused by a change in the accommodative stimulus, the (A-C)/A ratio, was determined for 10 non-presbyopic subjects before and at periodic intervals after homatropine was instilled in both eyes. The fixation disparity technique for measuring motor imbalances, as described by Ogle, Mussey, and Prangen,[9] and by Ogle and Prangen,[10] was used, because this method demands binocular vision and binocular coordination with fusion during the tests. This experimental procedure has shown that even if the convergence is not free to act, the innervations for a change in convergence due to a change in the stimulus to accommodation are present, for the existence of a change in the disparity shows that the binocular imbalance is altered.

APPARATUS

All the tests were made for a near visual distance of 33 cm., corresponding to an accommodative stimulus of 3 D. and to a convergence of 3 meter angles. The subject views through a phorometer adjusted before the eyes a negative photographic transparency plate, illuminated from behind and mounted in a suitable box. On the plate is a pattern of Snellen-like letters seen on a black background. These letters provide a 12-degree visual field, within which there are, therefore, adequate stimuli for fusion and for accommodation. At the center of the plate, where there are no contours to stimulate fusion, a vernier or nonius device, consisting of two short vertical transparent lines, is provided. Behind these are attached Polaroid filters. These lines are so oriented that, with Polaroid plates before the phorometer, the upper of the nonius lines can be seen only by the right eye, the lower only by the left eye. The upper line is stationary; the lower line can be displaced horizontally by a suitable screw operated by the experimenter. The amount of displacement is indicated on an appropriate dial. By means of a shutter and cable release, the lower line can be exposed for any period of time. Rotary (Risley) prisms or ophthalmic lenses or both can be conveniently placed before the eyes of the subject (Fig. 1).

In the test the experimenter instructs the subject to look at the upper vernier line, and then the lower line is exposed for a fraction of a second. The subject is asked to report whether the momentarily seen line appeared to the right of, to the left of, or centered with, the upper line. Between exposures the lower line is adjusted to a new position. The limits of the range within which the lower line can be displaced and the subject can report that the two lines appear one directly below the other are obtained. The distance or the horizontal displacement between the stationary line and the midposition of the range of movement of the lower line is the fixation disparity. This is recorded as the angle (in minutes of arc) subtended by this linear disparity to the subject. If a motor imbalance (a lateral phoria) exists under the conditions of observation, a fixation disparity will be measured. This disparity shows that, in spite of the details for the stimulation of fusion, the true point of convergence is slightly in front of the target if an esophoria is present (a disparity taken positive), or is slightly in back of the target if an exophoria is present (a negative disparity). The greater the imbalance, the greater the disparity becomes.

Subjects with good visual acuity in both eyes and with a low degree of muscle imbalance can usually make the discrimination within 1 minute of arc. It will be clear that, in this test, fusion is prevented at the center of the plate and that, at the instant the fixation disparity is measured, the images are fused extrafoveally. The subject is permitted, however, to look about the target between measurements. The phenomenon, however, is the same irrespective of this fact. The actual magnitude of the disparity might be less if the fused images included more of the foveal regions.[9]

PROCEDURE

To obtain the necessary data for this study, two separate sets of measurements are required. First, the change in fixation disparity must be found when the eyes are forced to converge or diverge with rotary prisms placed before them, and, second, the change in fixation disparity must be determined when the stimulus to accommodation is changed with spherical ophthalmic lenses placed before the eyes. Each set of data when plotted yields a curve characteristic of the subject's particular ocular behavior.

In the first set of measurements, the disparity is determined normally, and then the eyes are forced to converge or diverge by placing prisms alternately base out and base in, in steps of 4 Δ (or sometimes less, as needed). The time taken to obtain a reliable measurement of disparity

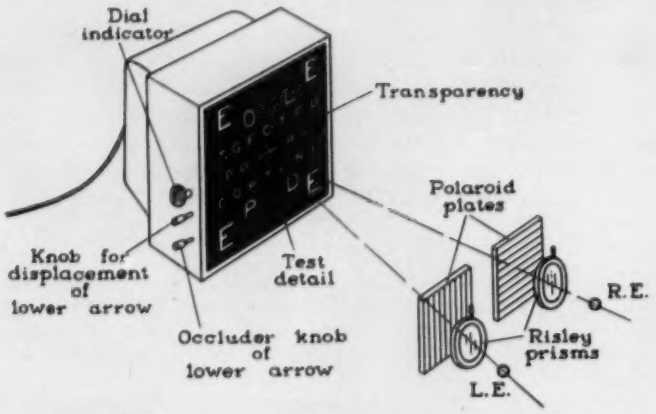

Fig. 1.—Schematic drawing of the apparatus used to measure fixation disparity at a near visual distance. From "Researches in Binocular Vision," by K. N. Ogle, reproduced by permission of W. B. Saunders Company, Philadelphia.

with each prismatic deviation is made as brief as possible and about the same each time. This tends to prevent any significant compensatory effects.[18] The alternation of base out and base in tends to prevent cumulative tonicity of the extraocular muscles from affecting the results. Even this procedure sometimes leaves a residual effect.

In the second set of measurements, spherical ophthalmic lenses are placed before the eyes, alternately minus lenses to increase the stimulus to accommodation and plus lenses to decrease the stimulus to accommodation, in steps of 1 D., or less if needed.

Typical curves are shown in Figure 2*A* and *B*. Figure 2*A* shows the effect on the motor imbalance, as measured by the fixation disparity, when the convergence is changed with constant stimulus to accommodation. On the abscissa are the meter angles of forced convergence (positive) or divergence (negative) in meter angles (meter angle=diopters of prism introduced divided by interocular separation in centimeters). On the ordinate is the measured fixation disparity in minutes of arc, esodisparity (overconvergence) positive and exodisparity (underconvergence) negative. A smooth curve has been drawn through the points.

Fig. 2*B* shows the similar curve when the change in stimulus to accommodation is plotted on the abscissa positive to the right (minus spheres) and negative to the left (positive spheres).

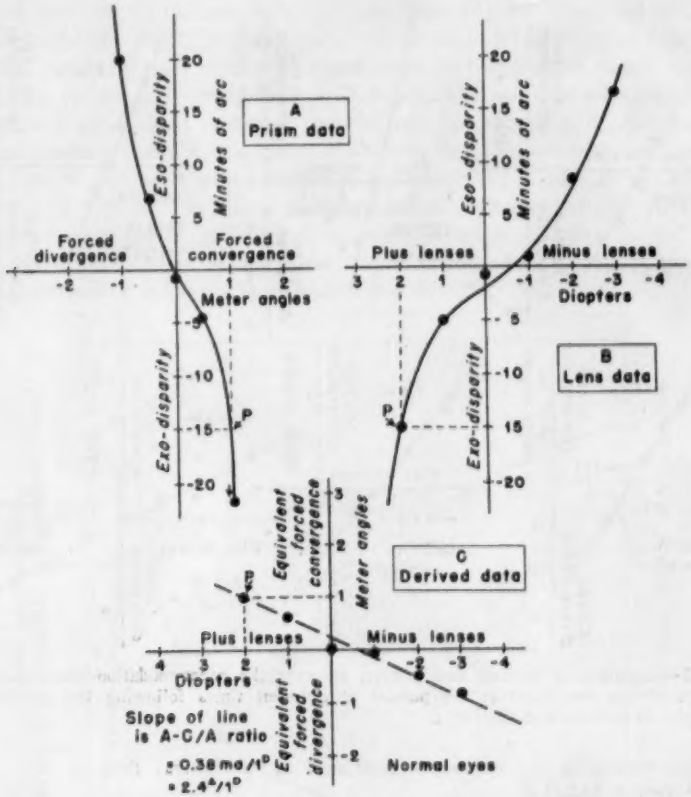

Fig. 2.—Normal fixation disparity curves for Subject 1. *A*, curve obtained when the eyes are forced to converge or diverge by prismatic intervention; *B*, curve obtained when the stimulus to accommodation is changed with plus or minus spheres; *C*, the derived curve from *A* and *B*, relating the change in stimulus to accommodation to the equivalent change in the forced vergence.

To find the quantitative relationship between the change of stimulus to accommodation and the accommodative convergence, a third set of data (Fig. 2*C*) is derived from the curves shown in Figure 2*A* and *B*. The procedure is as follows: Since the fixation disparity is a measure of the motor imbalance, one must find that particular forced convergence (or divergence) that causes the same imbalance (fixation disparity) as does each of the changed stimuli to accommodation. For example, one may consider Figure 2*B*, in which it is shown that a +2 D. sphere before each eye causes an exodisparity of 15 minutes of arc. Going now to Figure 2*A*, it is found by interpolation on the curve that an exodisparity of 15 minutes of arc is also caused by a forced prismatic deviation of about 1 meter angle. Thus, in Figure 2*C*, for the lens power 2 D. on the abscissa, the 1 meter angle is plotted on the ordinate. When this procedure is repeated for all the spherical lenses used, there is obtained a series of points on the graph (Fig. 2*C*) which, as has been shown before,† fall fairly well on a straight line. The line which best fits the data is then drawn on the graph. The slope of this line (change in equivalent forced convergence corresponding to a given change in stimulus to accommodation) is the ratio of the accommodative convergence to the accommodation—the (A-C)/A ratio abbreviated. In Figure 2*C*, this slope is 0.38 meter angle per diopter of change in accommodative stimulus (written 0.38 ma/1 D.). To express this in prism diopters, one merely multiplies the

† References 10 and 11.

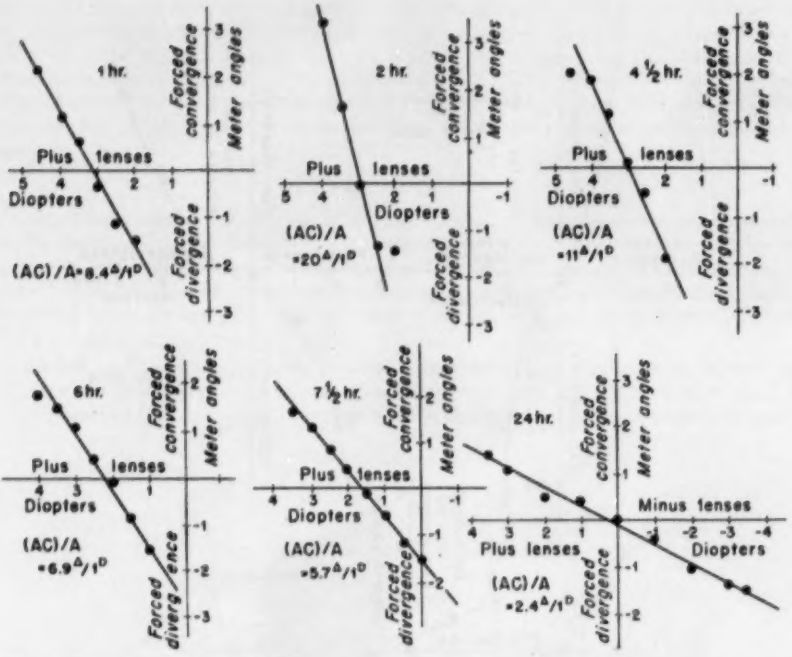

Fig. 3.—Sequence of derived data curves, showing the accommodation-convergence ratio (the slope of the line fitted to the points) at different times following the instillation of homatropine in both eyes of Subject 1.

meter-angle finding by the interocular separation, in centimeters; thus, in this case the (A-C)/A ratio is 2.4△/1 D.

In this study, first the normal (A-C)/A ratio was determined from at least two sets of data. At the beginning of the experiment proper, 2 drops of 2% homatropine hydrobromide were instilled in each of the subject's eyes. Ten minutes later 2 more drops of 2% homatropine hydrobromide were instilled. The (A-C)/A ratios were then obtained at certain intervals of elapsed time after the second instillation, and the determination was continued until the (A-C)/A ratio had returned to normal, or nearly normal. No attempt was made to obtain a complete cycloplegic effect. The near point of accommodation was also estimated by the "push-up" method, using the Duane line.

RESULTS

Ten nonpresbyopic persons served as subjects for this study. The detailed results for one subject, which are typical of the group, are shown in Figure 3, which gives the curves for the derived data only.

Inspection of these sets of data shows that, first, the slope of the line in the derived graphs, which gives the (A-C)/A ratio, increases markedly during the early phases of the homatropine action, as noted first by Maddox ‡ in 1893; and, second, that the points describing the derived data tend to fall on a straight line throughout the entire range of change of accommodation stimuli (lenses).

When the (A-C)/A ratios obtained from these derived graphs are plotted against the time elapsed since the last instillation of homatropine, one obtains the curve shown in Figure 4. The time is represented on the abscissa, in hours; the

‡ Maddox, E. C., cited by Morgan.[7]

(A-C)/A ratio, on the ordinate axis, in prism diopters per 1 D. change in stimulus to accommodation. This curve is similar to an absorption-clearance type curve. The (A-C)/A ratio rises rapidly to a maximum and then more slowly decreases, approaching the normal value in about 25 hours. The maximal effect appears for most subjects after about one hour, but for one subject (Fig. 4) the maximum occurs at about two and a half hours. This time duration is much longer than is usually thought necessary for a complete cycloplegic effect to occur. Van der Hoeve and Flieringa [14] found the loss of accommodation with homatropine paralysis to have a very steep ascent, with maximal effect in about 30 minutes, and a slow descent, requiring almost 24 hours for the accommodation to return to normal. They found cocaine to have a steep ascent and descent.

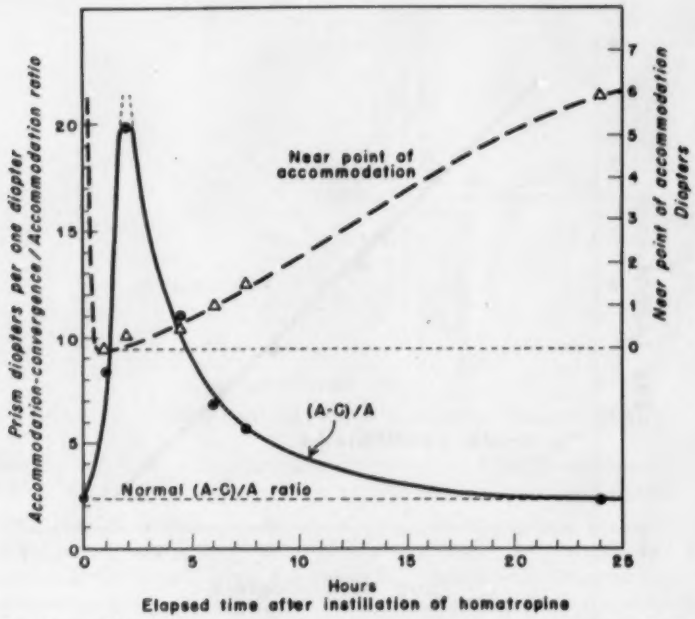
Prism diopters per one diopter Accommodation-convergence / Accommodation ratio
Near point of accommodation Diopters
Near point of accommodation
(A-C)/A
Normal (A-C)/A ratio
Hours
Elapsed time after instillation of homatropine

Fig. 4.—Curve showing the course of the (A-C)/A ratio and the near point of accommodation following the instillation of homatropine in the two eyes.

The data for the near point of accommodation estimated by the "push-up" method, using a Duane line, are also illustrated on the same graph (Fig. 4), which shows a maximal cycloplegic effect after about one hour. Whether this difference in the time periods for maximal effects is significant is uncertain as yet.

The maximal (A-C)/A ratio found for Subject 1 in Figure 4 was about 20Δ/1 D. The magnitude of this ratio probably depends on whether the maximal cycloplegia has been attained or not. Morgan [15] reported that for a complete cycloplegia in only one eye the (A-C)/A ratio measured by phoria tests became nearly infinite. The present data do not suggest so great a change, but it must be remembered that the time consumed in obtaining the complete data by the technique described here was seldom less than 15 to 20 minutes. Nor is it known that complete cycloplegia was obtained in these experiments, since emphasis was not placed on this point.

The magnitude of the (A-C)/A ratio is certainly related to the degree of cycloplegia, as estimated by the near point of accommodation. For the data of Subject 1, in the recovery part of the curve, the (A-C)/A ratio above the normal value appears to be inversely proportional to the near point of accommodation (Fig. 5).

More important than the increase in the (A-C)/A ratio with homatropine in both eyes and the fact that this increase is related inversely to residual accommodation present is the fact that there is a proportional convergence response to a given change in the stimulus to accommodation (caused by lenses), even though no (or practically no) actual accommodation is possible. Inspection of the derived data curves in Figure 3 shows that the convergence response is proportional to the change in lens power, since the derived points all fall on a straight line. Thus, it is

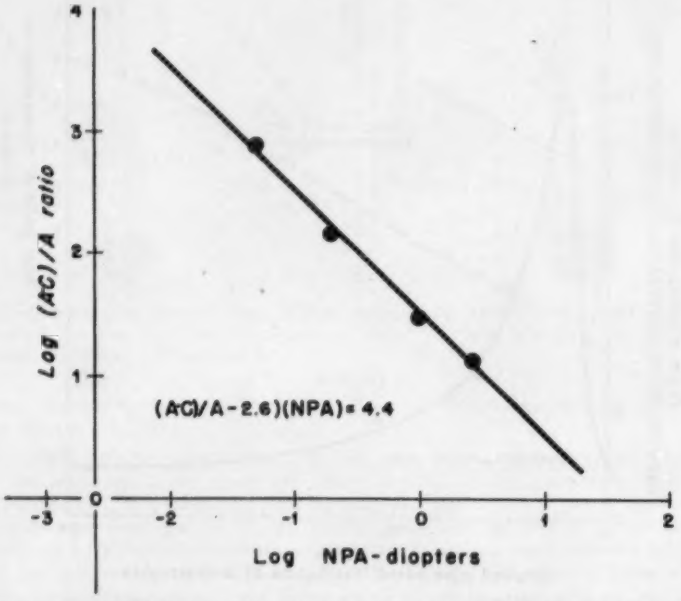

Fig. 5.—Relationship between estimated near point of accommodation and the (A-C)/A ratio.

the stimulus to accommodation (as well as the actual accommodation, that is, the state of contraction of the ciliary muscles) that gives rise to the accommodative convergence.

The same linear type of relationship has also been found in patients with complete presbyopia. Figure 6 illustrates the data of one such subject, who was 70 years of age. Here the derived data again can be described by a straight line, in spite of the fact that no accommodation could occur and the retinal images became increasingly blurred as the lens power was increased both plus and minus. According to Fincham,§ the stimulus for an accommodative change does not occur if the blur caused by lenses exceeds 1¼ D. This result is consistent with the derived data of several of the subjects, in that the derived data tended to depart

§ References 16 and 17.

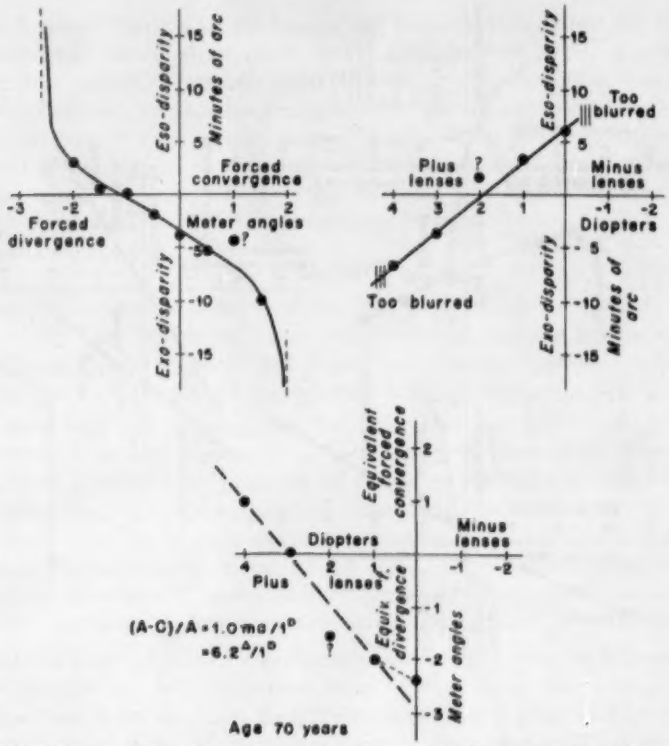

Fig. 6 (Subject 2).—Fixation disparity data for a completely presbyopic subject.

from linearity (to level off) when the difference in lens power became greater than about 1½ D. However, it is clear that, with this restriction in mind, these data show that the magnitude of the accommodative-convergence synkinesis is proportional to the change in stimulus to accommodation, whether the eye actually has accommodated or not. Thus, the synkinesis must result from the innervation for a contraction of the ciliary body—an innervation which is therefore directly proportional to stimulus to accommodation. This is to say, a unit change in the stimulus to accommodation results in a unit change in the innervation to the convergence-divergence processes. The ratio of the accommodative convergence to the accommodation—the (A-C)/A ratio—for this presbyopic subject (Fig. 6) is 6.2Δ/1 D.

The third result to be pointed out in this study is that for each subject (except one) the curve describing the relationship between fixation disparity and forced convergence and divergence is, on the whole, nearly identical for each set of data during the entire course of the homatropine procedure. The origin of each curve, of course, was not the same, but that depends on the particular spherical powers used before the eyes during the prism part of the test. In other words, the amplitude range between forced convergence and forced divergence, and the rate of change of imbalance remained nearly the same irrespective of the degree of cycloplegia. Figure 7 shows that the seven sets of data of one subject obtained during the initial phases and during the recovery period from the effects of homatropine can be superimposed.

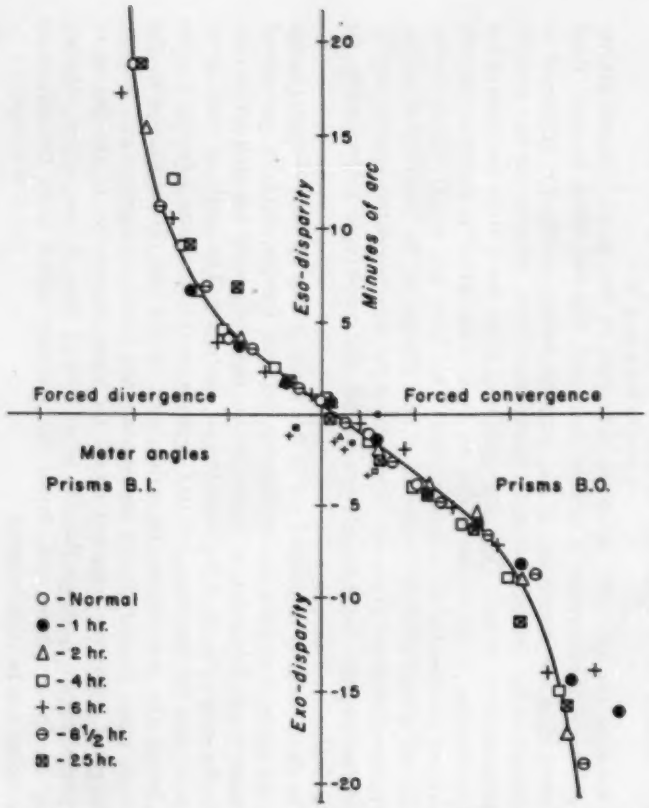

Fig. 7 (Subject 3).—Graph showing how the curves relating fixation disparity and forced convergence and divergence are essentially the same, irrespective of the degree of cycloplegia.

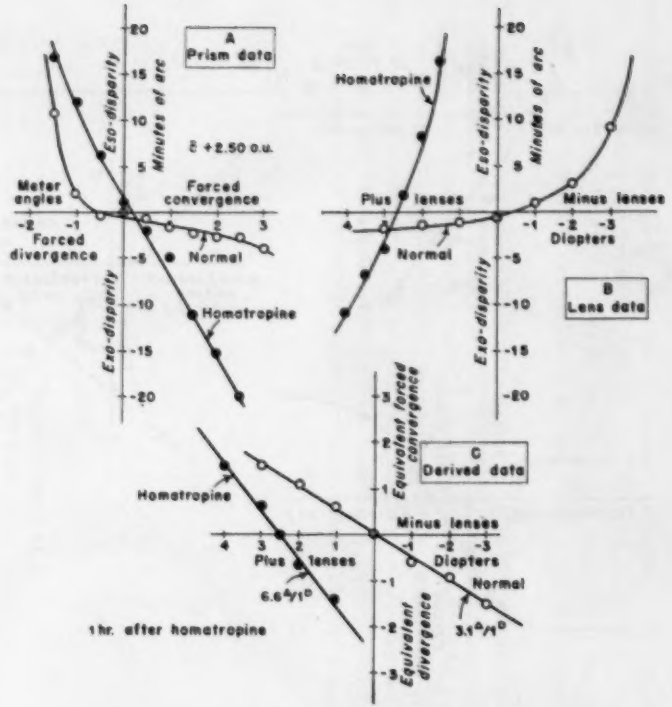

Fig. 8 (Subject 4).—Data of one subject for whom the curves describing the fixation disparity and the forced convergence and divergence are not the same when the eyes are under cycloplegia as when they are not under cycloplegia.

Figure 8 shows the data for the normal and for a time elapsed of one hour for the one subject of the 10 whose prism curves were different. These graphs show that when this subject's eyes are under the effect of homatropine, the rate of change of imbalance increases markedly over his normal rate when the eyes are forced to converge or diverge with prisms. It is possible, however, that even for this subject the end-points of the range of amplitudes of the prism vergence of the various sets of data are essentially the same, in spite of this variation of the rate of change of disparity with homatropine cycloplegia.

COMMENT

In trying to account for these results, and in particular to account for the linearity in the accommodative convergence with change in the stimulus to accommodation, as well as other well-known facts, one must at present resort to some speculations. None of these are, however, entirely satisfying.

One must take into account that the control of the accommodation reflex probably lies in cortical centers. The innervations to the ciliary muscles for accommodation changes must primarily be related to the blurring (out of focus) of the images falling on the retinas, and therefore the initial stimulus must be retinal. It is probable that the amount of the innervation may also originate here as responses to blurredness of images. At the same time, these responses may also be subject to the control of higher cortical processes, as most certainly occurs in the so-called "proximal" influence on both accommodation and convergence.

It would be expected that stronger innervations would be sent to ciliary muscles partially paralyzed by a cycloplegic drug, in an effort to cause some accommodative effect. This innervation would, by the accommodative-convergence synkinesis, result also in an increase in innervations for a convergence change. Thus one might anticipate an increase in the accommodative convergence with the eyes under cycloplegia. But, while one would expect a greater stimulus to the ciliary muscles in an effort to cause an accommodative change, one might accordingly expect the innervation to increase greatly, if not maximally, at once when the retinal images fail to clear.

Similarly, one might expect an increased accommodative convergence in presbyopic subjects, where, again, normal innervations to the ciliary muscles would not result in a clearing of the retinal image. The data do not show this type of response to be true. Rather, equal increments of convergence change occur with equal changes in the stimulus to accommodation. This is to say that the rate of change of the tonus of the ocular muscles for a change in convergence caused by a change in the stimulus to accommodation tends to be constant throughout the range of response. These increments of convergence are greatly increased when the eyes are under cycloplegia, but are normal in the presbyope.

On the basis of the results of this study, one must agree with Alpern [18] that the effect of age on the accommodative mechanism must be fundamentally different from the effect of drugs which partially paralyze the ciliary muscle. When the ciliary muscle becomes partially paralyzed (by a cycloplegic), not only does the eye lose its ability to accommodate, but the (A-C)/A ratio increases, and the amount of increase in the (A-C)/A ratio is an indication of the extent of paralysis of the ciliary muscle. No corresponding increase in the (A-C)/A ratio accompanies the inability of the eye to accommodate for near objects which is associated with increased age.

One may assume that the accommodative-convergence synkinesis consists of two processes, as was suggested in the third theory in the introduction. The first of the two processes, like an unconditioned reflex, is the normal physiologic association—probably unalterable and persisting throughout life—in which the amount of ciliary contraction for each given change in stimulus to accommodation is the same. The second of the two processes is to be compared to a conditioned reflex and is subject to change or adaptation with environmental stress. Thus, when the ciliary muscles are "rapidly" paralyzed with a cycloplegic drug, both processes are active and the innervations to the muscles are increased through the increased activity of the second process. In presbyopia, in which the decrease in the ability of the lens to change its shape takes place so slowly with age, the second process becomes less operative, and only the first predominates.

However, in order to explain the proportional increase of the (A-C)/A ratio throughout the range of change of accommodative stimuli when the eyes are under the influence of a cycloplegic, one would have to assume further that the second process acts as an "amplifying device" for the basic quantified innervations originating from retinal stimulation and ciliary response. It would seem, moreover, that if a conditioned-reflex-like process were normally active, the complete (A-C)/A ratio for normal subjects would be nearer 6.3 Δ per 1 D. of accommodative-stimulus change, which is the amount of convergence actually related to the accommodative stimulus in use all the time, rather than the 3.0 to 3.5Δ per 1/D. generally found.

To account for the results, one might assume, in a different line of thought, that the accommodation-convergence association is basically an unconditioned-reflex-like association brought about by excitatory and inhibitory innervations acting simultaneously. Through interference by the cycloplegic drug, the inhibitory innervations would be depressed, so that the effect of the excitatory part of the association constitutes a larger stimulus, and thus the (A-C)/A ratio increases. The more complete the cycloplegia, the more the inhibitory part of the association is depressed. Such an assumption may, however, imply some kind of afferent communication from the nerve processes in the ciliary bodies.

On the basis of the results for 9 of the 10 subjects studied, it would appear that the pattern of motor imbalance caused by forcing the eyes to converge or diverge with prisms tends to be unaffected by the cycloplegia. Perhaps one might infer from this that any stimulus for a convergent accommodation has no reciprocal effect on the convergence through the accommodation-convergence association.

SUMMARY

The ratio of the accommodative convergence to an accommodative-stimulus change, the (A-C)/A ratio, increases markedly with increasing degrees of cycloplegia produced by homatropine. The (A-C)/A ratio, above the normal value, appears to be related inversely to that part of the accommodation unaffected by the cycloplegia.

At a given state of cycloplegia, the (A-C)/A ratio varies linearly with the change in stimulus to accommodation, within limits of about ±1½ D. The pattern of change in muscle imbalance with changes of forced convergence or divergence produced by prisms base out or base in tends to be the same irrespective of the state of cycloplegia. This implies that the range from base-in to base-out end-points, or the fusional amplitude, tends to be constant. The marked increase in the

(A-C)/A ratio with homatropine cycloplegia must be due to a different mechanism than is present in complete presbyopia, where the (A-C)/A ratio remains more or less normal.

Possible theoretical bases to account for the results are discussed.

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Aqueous Humor Outflow: An Experimental Study Using Radiopaque Materials

I. Paracentesis Technique, Response Evoked, and Demonstration of Pathway of Outflow

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In 1941 Ascher * first detected aqueous veins biomicroscopically. They have since been photographed † and observed in experimental animals.‡ Goldman § concluded that these veins, connecting the intrascleral venous meshwork with the episcleral venous meshwork, contained aqueous by the observation that they remained colorless after intravenous administration of the dye fluorescein sodium (uranin). The episcleral vessels, however, contained blood and took on a yellowish-green tint. This same investigator repeated Seidel's (1923) rabbit experiments by injecting India ink into the anterior chamber of a sarcomatous human eye. He reported that the episcleral vessels did not change color but that the aqueous veins were tinted black. It was felt that this demonstrated the communication of the anterior chamber with the aqueous veins.

More recent work by Greaves and Perkins,[9] however, has revealed a failure of suspensions of India ink to appear in the aqueous veins of rabbits after injection into the anterior chamber. These investigators demonstrated the communication between the anterior chamber and the aqueous veins in rabbits by the use of Evans blue, a nonparticulate, water-soluble dye, which does appear rapidly in the aqueous veins following its injection into the anterior chamber. Their conclusion was, in part, that this connection "does not allow the passage of particles of size approximately 1μ."

Up to the present time there have been three instances of the use of particulate, radiopaque materials in the study of aqueous humor outflow. Baltin,[12] in 1945, repeated Croci's (1932) experiment by injecting Thorotrast, a suspension of thorium dioxide particles, into the anterior chamber of rabbits. On roentgenoscopic examination the normal pathway of aqueous outflow was not observed. The

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* References 1-3.

† References 4-6.

‡ References 7-9.

§ References 10-11.

radiopaque material was seen to be gradually absorbed, passing into the suprachoroidal space and invading the iris stroma. Histologic examination revealed the particles being carried away by histiocytes.

The size of the particles which made up Baltin's Thorotrast suspension was evidently so large that the particles were prevented from following the normal pathway of aqueous outflow, thus necessitating removal of the foreign material by phagocytosis. The particle size of Thorotrast suspensions varies from one preparation to another. An electron microscope study || of a preparation of Thorotrast (Testagar & Co., Inc.) revealed the particle size to be 7μ to 10μ. On the other hand, in a very recent experiment, François, Neetens, and Collette [13] employed a number of suspensions of particulate, radiopaque materials in an investigation of the orifices of the inner wall of Schlemm's canal. Among the suspensions which were injected into the anterior chambers of monkeys in vivo and of men immediately after death was a Thorotrast (Heyden Chemical Corporation) preparation which contained particles only 0.1γ in size. From the results of their microradiograms they concluded that the orifices were greater than 1.5γ and smaller than 2.25γ in diameter. However, their technique disrupted the delicate physiologic mechanism of aqueous drainage, since it entailed replacement of the aqueous which was aspirated by a quantity of radiopaque material in excess by 33% to 50% and subsequent amputation of the anterior segment, dissection, fixation, and slicing before exposure of the films.

PARACENTESIS TECHNIQUE

In the present experiment three different, water-soluble (nonparticulate) radiopaque substances were injected into the anterior chamber of rabbits. The materials used were sodium acetrizoate 30% (Solution Urokon Sodium 30%, Mallinckrodt), 18 injections; diatrizoate sodium 50% (Hypaque Sodium 50%, Winthrop-Stearns), 8 injections, and sodium iodipamide 20% (Cholografin Sodium 20%; disodium salt of N, N'-adipyl-bis [3-amino-2,4,6-triodobenzoic acid], Squibb), 3 injections.

The paracentesis technique employed was a modification of the method of Amsler and Verrey.[14] Albino rabbits weighing 2.5 to 4.5 kg. were anesthetized, and, after the eye was fixed by the superior rectus, a 30-gauge needle, attached to an empty tuberculin syringe, was introduced into the sclera 3 to 5 mm. behind the limbus, near the point of fixation. The needle was then directed in an oblique, "sclera-splitting" course into the anterior chamber. A second needle, attached to a tuberculin syringe containing 0.3 cc. of the radiopaque material to be injected, was introduced a short distance away by the same technique. Into the first syringe was drawn 0.3 cc. of aqueous humor. After the needle attached to that syringe was carefully removed from the chamber, the contents of the second syringe were slowly injected, refilling the chamber. In the other eye, the control, an identical procedure was employed except that, after withdrawal of the aqueous, that aqueous was reinjected into the chamber.

The use of the "sclera-splitting" approach is important for two reasons. In the first place, the use of a larger needle and a more direct approach to the chamber through the limbus resulted in leakage of part of the contents of the chamber after withdrawal of the needle. This is avoided by the production of a needle pathway of smaller diameter and so situated that the resiliency of the scleral tissue and the outward lines of force exerted by the intraocular pressure quickly collapse it. In the second place, it is felt that the four instances of corneal reaction observed occurred when the needle was introduced too near the limbus, thus giving the radiopaque substance access to the cornea at that point. No corneal reaction was encountered when the indirect needle pathway through the sclera was employed.

RESPONSE OF EYES TO TECHNIQUE AND RADIOPAQUE MATERIALS

Evaluation of the reaction of rabbit eyes to any procedure or substance must be tempered by the knowledge that these eyes are very responsive as compared

|| Carrington, R.: Personal communication to the author.

with human eyes. Rabbit eyes characteristically exhibit aqueous flare, dilatation of the iris vasculature, and iris edema on the slightest provocation.¶ Tonometric, slit-lamp, and histologic examination of both control and test eyes resulted in the establishment of a base line response, that is, a reaction which was consistently elicited in both groups by an identical paracentesis technique. This anterior chamber response in the rabbit may be due to a mechanical lack of tone following aspiration, or might well be explained as a result of a vasodilatatory nervous reflex, as described by Duke-Elder and Duke-Elder.[16] In any event, the following responses were observed in both control and test eyes:

Tonometric Examinations.—Serial tonometric measurements revealed that, after a short latent period, there was a rise of intraocular pressure from normal levels, followed by a fall to normotensive levels on the days following the initial procedure in both groups of eyes. Significant quantitative differences in intraocular pressures in the control eyes as compared with the test group were not evident.

Slit-Lamp Examinations.—Multiple examinations of every eye in both groups revealed aqueous flare, dilatation of the iris vasculature, and iris edema. There was rapid and spontaneous reversal of these changes.

Histologic Examinations.—Specimens taken from both groups at varying intervals displayed only dilatation of iris vasculature and iris edema in the early postparacentesis period. In no case at any time was there evidence of an active inflammatory process. No ocular foreign substance was identified. Histologic examination, therefore, revealed virtually identical, nonspecific responses in both groups of eyes.

If the responses of the two groups of eyes were similar in many ways, in what ways did they differ? The test group of eyes, in addition to exhibiting the above-mentioned changes, also reacted in the following manner:

Slit-Lamp Examinations.—Early formation of posterior synechiae was observed in many of the test eyes within a few hours after injection of the radiopaque material. These synechiae cleared completely without treatment within a few days to two weeks, a somewhat longer period than that required for disappearance of vessel dilatation and aqueous flare. Repeated injections of the test substances into the same eyes after recovery resulted in identical responses.

Corneal Changes.—In four of the test eyes (this experiment consisted of a total of 29 injections of radiopaque materials) an observable corneal reaction occurred, probably as a result of a needle pathway too near the limbus. In these eyes a small, very white area appeared in the cornea nearest the point of entrance within a few minutes after removal of the needles. This was followed, within the next hour, by generalized corneal edema. Microscopic examination of three eyes removed, respectively, 24, 48 hours, and 1 week following the injection revealed only the following mild, nonspecific changes: (1) a few scattered eosinophiles beneath the corneal epithelium; (2) poor staining of the peripheral layers of the cornea, and (3) in the first two eyes, loss of the corneal epithelium. In the fourth eye the corneal edema began to disappear after a few days. By the end of two weeks this opacification was resolved and the cornea was normal to slit-lamp examination and, subsequently, to microscopic study.

Interpretation of Response.—The eyes in both the control and the test group responded with an expected, nonspecific increase in capillary permeability: increased

¶ References 2 and 15.

intraocular pressure, typical plasmoid changes in the aqueous, and iris vascular injection or hyperemia. Changes attributable to the effect of the radiopaque materials injected could be detected only by biomicroscopy. The slightly greater response evoked in the test group was probably due to an assumed superimposed mild chemical iritis. In view of the mildness of the reaction of the rabbit eyes to the radiopaque materials, future investigations on these substances might well include their injection into the eyes of humans for which enucleation is proposed.

ROENTGENOGRAPHIC TECHNIQUE

Position.—Immediately after injection of the radiopaque material, the rabbit was placed on its back on the x-ray table with its neck extended so that the ears were beneath the back of the neck and the flat of the head rested on the table. The head was turned very slightly away from the test eye so that the bones of the skull did not obscure the film image of the eye structures. Thus perfectly perpendicular positioning of the eye was sacrificed. The superior pole of the eye was now closest to the film—that is, most inferior with the animal in this position. The center of the eye was 2 to 3 cm. from the film. The eyes were not proptosed, nor were the lids retracted.

Film.—Occlusal type (paper-backed, dental-size) film was used. It was placed flat on the table.

Technique.—A number of series of films were exposed, using a 2 mm. focal spot tube at a distance of 36 in. The exposure time was one-half second at 60 kv. and 200 ma. In an attempt to obtain greater detail, a 0.3 mm. focal spot tube was employed later in the course of the experiment. The tube limitation of 20 ma. necessitated a two-second exposure time. A tube-to-film distance of 36 in. and 78 kv. were used in these exposures. The long exposure time partially defeated the objective in using this tube, since its failure to stop the motion of the breathing animal often impaired the quality of the films.

Processing.—Routine processing was used throughout. The developing time was three minutes.

PATHWAY OF AQUEOUS OUTFLOW

The structures at the angle of the eye of a series of mammals were studied by Troncosco and Castroviejo,# using both slit-lamp and microdissection techniques. These studies revealed in rodents the absence of the canal of Schlemm, which is so conspicuous in higher mammals. They described in the rabbit a "cleft between the sclera and the outer side of the ciliary body which is partitioned by fibers of the pectinate ligament into several cavities filled with aqueous and communicating with the anterior chamber through the so-called Fontana's spaces." The name "ciliioscleral sinus" was given to this cleft.

Figure 1 is placed first because it demonstrates the anterior chamber filled with radiopaque material. However, with respect to the ciliioscleral sinus, Figures 2 and 3 are of interest. Figure 2 is an enlarged photograph of a film of the anterior chamber exposed two minutes following injection of 30% sodium acetrizoate. The angle is relatively sharp, with just the slightest trace of ciliioscleral-sinus filling. The film exposed four minutes later, Figure 3, demonstrates the same angle with the sinus now well filled with the radiopaque material. The hazy projection of the sinus on the film probably represents its trabeculation by strands from the pectinate ligament.

References 17 and 18.

Figure 1 is an eight-minute postinjection exposure of the eye of a second animal. This film demonstrates roentgenographically the outflow of radiopaque material through the aqueous veins. The veins begin just anterior to the angle and flare backward to the episcleral venous meshwork, where the contents are rapidly diluted with blood. The appearance of the radiopaque cone instead of isolated vessels is simply a result of the failure of the x-ray beam to resolve each minute radiopaque stream because of the too-broad area of origin of the beam from the tungsten plate. This superimposition of vein shadows might be compared to the solid cone of strands observed when one looks at a spider web in profile. Maintenance of the vertical axis of the eye in a vertical position allows one to obtain the

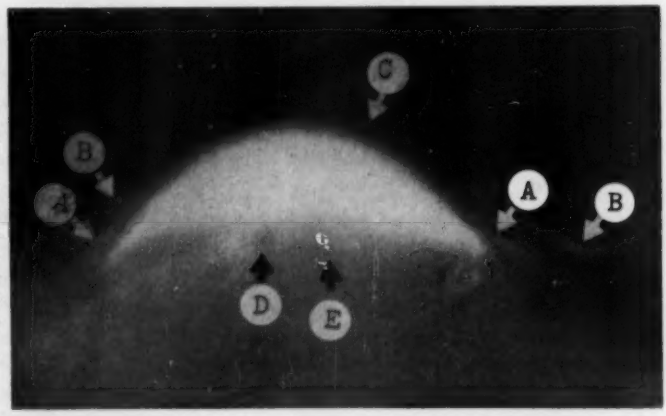

Fig. 1.—Eight-minute film. Anterior chamber of rabbit eye filled with acetrizoate. *A*, *A*, aqueous veins; *B*, *B*, lid soiling with radiopaque material; *C*, corneal shadow; *D*, air bubble in anterior chamber; *E*, hazy projection of angle.

Fig. 2.—Two-minute film. Arrow on left, sharp angle. Arrow on right, hazy projection of angle.

Fig. 3.—Six-minute film. Arrow on left, filling of ciliioscleral sinus. Arrow on right, hazy projection of angle.

superimposition of the aqueous veins, since most of them are located between the 2 and 4 o'clock and 8 and 10 o'clock positions.[3] The fact that there was leakage from the chamber after withdrawal of the needles is indicated by the presence of lid soiling with radiopaque material. Subsequent modification of the technique eliminated this evidence of leakage.

There is one very small air bubble in the anterior chamber in Figure 1. This serves as a convenient point of reference in quantitative studies. It is also useful in the explanation of the haziness which is often seen posterior to the most intensely white area. The bubble has risen to the highest point in the anterior chamber, with the animal in the position previously described. Figure 4 illustrates this diagrammatically. The point to which the bubble rises is the highest point of the angle.

Since the angle is much narrower than the main body of the chamber and can accommodate only a thin film of radiopaque material, it projects as a hazy whiteness. Since the vertical axis of the eye is tipped backward from the perpendicular to avoid the skull, that part of the angle containing the air bubble consequently projects behind the main body of the chamber. Close examination of Figures 2 and 3 reveals the same hazy projection of the angle.

Figure 5 is the 31-minute film of still another eye. It demonstrates filling of both the anterior and the posterior chamber as a result of diffusion of the radiopaque

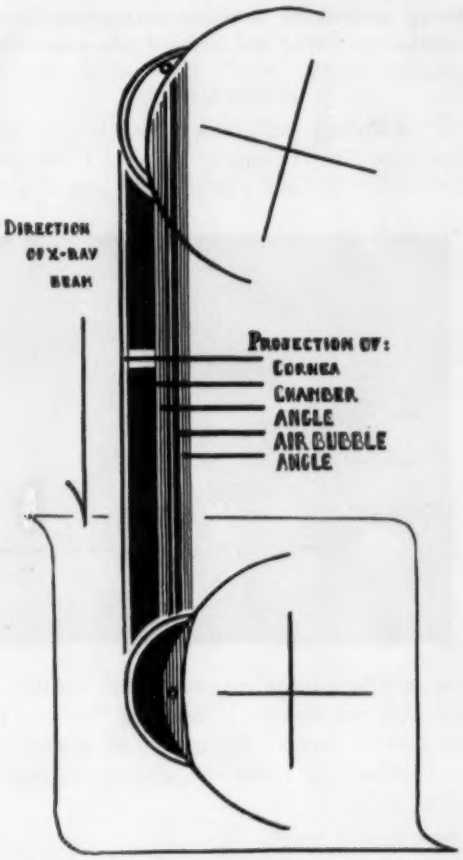

Fig. 4.—Diagram of position of eye filled with radiopaque material and small air bubble, above. Labeled degree of absorption of x-rays by different portions of eye. Corresponding areas on film, below.

substance behind the iris into the posterior portion of the aqueous chamber. An iris shadow and cast of both chambers can be seen.

An animal which was perfectly still and perfectly positioned was essential in order to obtain films which adequately demonstrate the minute structures illustrated in the photographs included here. Therefore, these structures were not visible in each film of every series. Although the structures shown here did appear generally in the sequence presented, the exact timing of these films is of limited significance.

The aqueous veins are minute vessels, and their shadows will appear on the films only as long as the concentration of the contrast media in them is great enough to absorb the x-rays. In the present study they have been seen as early as two minutes after injection. In one series, in which only 0.2 cc. of diatrizoate sodium was injected, with considerable leakage, as revealed by lid soiling, there was visualization of the vessels up to one hour after injection. How close this drainage of radiopaque materials is to the normal cannot be determined from these qualitative studies.

This brings us to the consideration of the quantitative aspects of outflow of radiopaque substances from the anterior chamber. A study which consists of obtaining and analyzing quantitative data and interpreting their implications with respect to aqueous outflow in normal and diseased eyes is now in progress.

CONCLUSIONS

The technique of introducing radiopaque materials into the anterior chamber of rabbit eyes is described. The response of the eyes to the control procedure of entering the chamber and to the test procedure of injecting three water-soluble radiopaque substances into the anterior chamber, as determined with the tonometer, the slit-lamp, and histologic examination, is discussed. The path of aqueous outflow in the rabbit from the anterior chamber through the ciliosclera sinus to the aqueous veins is illustrated. A subsequent paper will discuss the quantitative aspects of this study.

Fig. 5.—Thirty-one-minute film. Diffusion of substance into posterior chamber. *A*, anterior chamber; *B*, iris shadow; *C*, posterior chamber.

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Filter-Paper Electrophoresis of Tears

II. Animal Tears and the Presence of a "Slow-Moving Lysozyme"

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Goldsworthy and Florey [1] studied the lysozyme content of the tears of several species of animals. They used the reduction in turbidity of a suspension of Micrococcus lysodeikticus as a measure of the amount of lysozyme. They showed the absence of lysozyme in the tears of the cat and the rabbit. The tears of the goat and the dog had a small amount of lysozyme, which was about 100 to 1000 times less than the amount in normal human tears. It has been shown previously [2] that the tear fluid from a single subject may be analyzed by filter-paper electrophoresis. This method shows both the lysozyme component, which appears as a distinctive protein moving toward the cathode, and the other protein components of tears. Although there has been no report on the different protein components of tears of animals, Geinitz [3] studied the proteins of the blood serum of animals by means of filter-paper electrophoresis. He showed that the serum proteins are similar from animal to animal, although there are minor differences both qualitatively and quantitatively.

A comparative biochemical survey of various animal species was undertaken with the following points in mind: 1. Are the tear proteins as similar from animal to animal as are the serum proteins? 2. Is the presence of high concentration of lysozyme in human tears unique among the species? 3. Is there any correlation between the tear proteins and the blood proteins?

ANIMALS *

Our survey includes representative samples of reptiles, birds, and mammals. The animals were normal, and at least two samples of tears were taken from each animal, although numerous samples were taken from the more available ones. The reptiles included the alligator (baby), desert tortoise, blue-tongued skink, and fringed iguana. The birds included chickens (male and female), turkey, and pigeon. The mammals were represented by the guinea pig, rabbit, cat, dog,

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* The following persons provided the animals not available at the Medical Center:

Dr. J. Slaven, California Academy of Sciences, Golden Gate Park, San Francisco; Mr. C. N. Baldwin, San Francisco Zoological Gardens; Dr. A. L. Black, University of California, Davis, Calif.; Dr. L. B. Tennison, Cutter Laboratories, Berkeley, Calif.; Mr. O. Grimle, Turlock Poultry Ranch, Turlock, Calif.; Mr. H. Christen, Christen's Dairy Ranch, San Francisco; St. Francis Riding Club, San Francisco.

pig, sheep, goat, cow, horse, Himalayan bear, Indian elephant, monkeys (rhesus and ring-tailed), and gibbon. Human tears were given for comparison.

METHODS

Two different methods of electrophoretic analysis were used. One was similar to the method described earlier,[2] with slight changes in the experimental conditions of the run. These conditions were as follows: phosphate buffer with 20% added ethylene glycol, pH=7.8 (ionic strength as measured in Serfass conductance bridge = 800μmhos/cm.); constant voltage = 3.2 volts/cm.; time of run = 16 hours. The second method employed a standard commercial apparatus.† The tears were absorbed on a 5 × 25 mm. indicator paper strip. The moistened paper, which holds about 1.6 μl/mm., is placed on the conventional filter paper strips in the apparatus, and the run is made under the following conditions: phosphate buffer, pH = 7; ionic strength (calculated) = 0.2; constant current = 25 ma.; time of run = 6 hours. Both methods used the standard bromophenol blue stain. All of the developed traces were scanned with a densitometer (Spinco Analytrol). This instrument records a trace the ordinate of which is a function of the density of the stain and the abscissa of which indicates linear distance.

For purposes of presentation, all the traces obtained by the first method described above were copied by tracing through translucent paper. This procedure averaged out small deviations. Larger "squiggles," usually apparent at the point of origin of the run, were not averaged out and are considered artifactual in that they resulted from removal, prior to scanning, of the paper disc upon which the sample was absorbed.

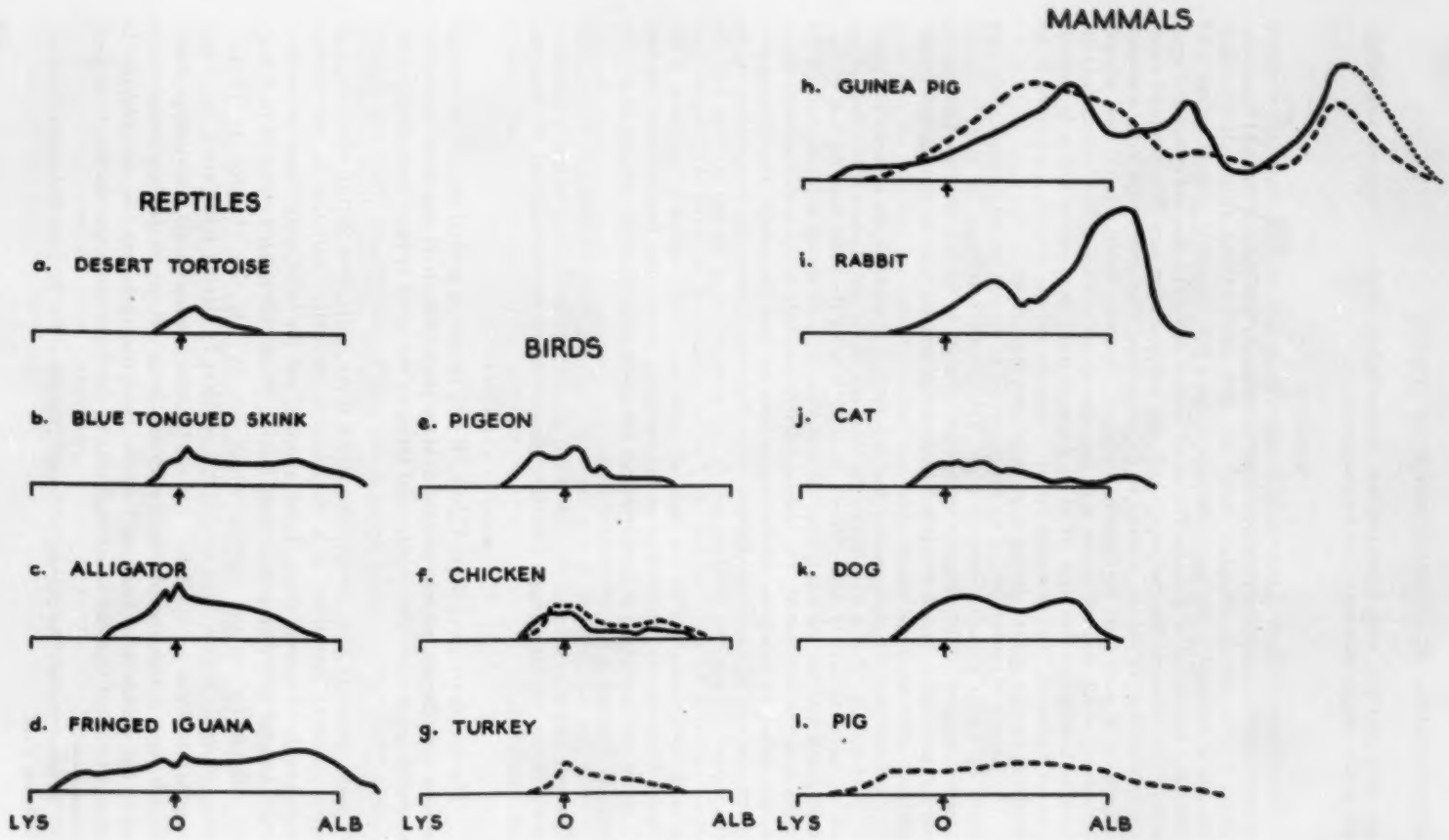
The traces from the second method described above, if presented in the same manner, would be on an entirely different scale because the conditions of the run (amount of material and the electrophoresis apparatus) were different. In order to bring the traces from the two methods more closely into line, the traces from the second method were altered to correspond with the traces from the first method. The translated traces were then traced onto translucent paper, using a dashed line to indicate that the original trace had been manipulated. The following procedure was used for translation: Original traces of a normal human tear were obtained by the two methods. It was then found empirically that an expansion of the loci of points from the second method in the x-axis direction of 1.7 and a contraction of the y-axis of 0.5 would result in rough correspondence of the two traces of human tears. This is shown in example *w* in the Figure. These same two factors were used in translating all the traces from the second method. It can be seen in the cases of the chickens (*f*) and guinea pigs (*h*), which were run by the two methods, that there is a rough correspondence.

These data are qualitative, as it is difficult to obtain quantitative tear samples from animals other than laboratory animals. The order of this quantitative difference may be seen in example *v* of the Figure. Two tear samples were taken from one subject and run separately, but under the same conditions.

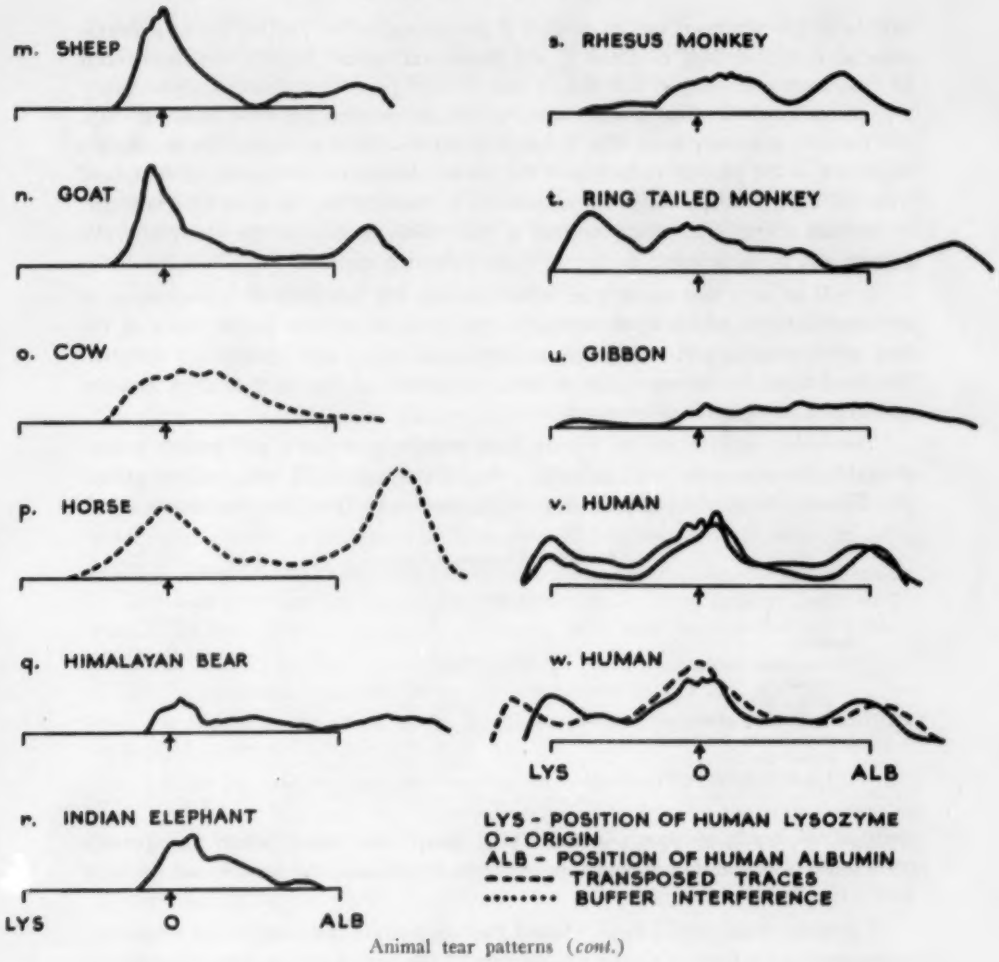
RESULTS AND COMMENT

The results are given in the Figure. It may be seen in general that all the animals have a considerable protein content in their tears. This is in the order of several tenths of a per cent. The reptiles and birds do not seem to have fast-moving components. Most of the protein moves slower than human albumin. The other animals in many instances have components which move faster than human albumin. It is quite apparent that there is a considerable qualitative variation in the protein components of animal tears. Land animals, for the most part, have to moisten their corneas with endogenous fluid (tears). Even this small amount of fluid may be difficult for certain reptiles, which live in hot, dry climates, to produce endogenously. Snakes have solved this problem by having transparent lids fused together to form a "spectacle" (Walls[4]), which requires no moistening. Some lizards have a transparent window in the lower lid which permits some vision when the eyelids are closed, and at the same time prevents loss of moisture. It should be noted that the usual explanations for these protective devices have been

† Loaned through the courtesy of Spinco Division of the Beckman Instrument Company, Belmont, Calif.



Animal tear patterns



Animal tear patterns (*cont.*)

pointed toward either mechanical protection against abrasion (Walls [4]) or radiation protection against strong sunlight (Williams and Hecht [5]). Conservation of moisture may be teleologically considered as another form of protection.

It will be noted that none of the animals has a cathodic-moving component which travels as far as human lysozyme (under these experimental conditions 42 mm. from the origin to the center of the spot). The ring-tailed monkey, rhesus monkey, and gibbon each have a component which travels about three-fourths as far (30 mm.) as human lysozyme. With different breeds of dogs we have occasionally found this same component. The tear fluids of the night monkey and the potto were analyzed electrophoretically, and this 30-mm. component was found in the night monkey in high concentration, similar to that in the ring-tailed monkey, but it was absent in the potto. These two animals died before their tears could be analyzed under standard conditions and included in the Figure. In order to see whether this 30-mm. component is a "slow-moving lysozyme," the activity of the tears of several of these animals was tested against M. lysodeikticus. A 24-hour-

culture of this organism was suspended in phosphate buffer (pH—7.0) to approximate an optical density of about 1, and the actual optical density was determined by colorimetric reading at 650 mμ. A dot of filter paper containing approximately 3 μl of tears was incubated with 10 ml. of this suspension for three hours at 30 C and the optical density read. The Table gives the results of this test. The results are expressed as the percent reduction of the optical density of the sample as compared with the control suspension. The sensitivity of the test has been so designed that an amount of egg-white lysozyme that is discernible visually on the electrophoretic pattern will be measurable by the turbidity reduction method.

It will be seen that an enzyme which reduces the turbidity of a suspension of M. lysodeikticus, which by definition is lysozyme, is present in the tears of the ring-tailed monkey and the rhesus monkey and is low and variable in different breeds of dogs. By inference, the 30-mm. component of the night monkey and the gibbon is a "slow-moving lysozyme."

Two other animals in the Figure have protein material which travels a considerable distance to the left (cathode): the fringed iguana, 28 mm., and the guinea pig, 27 mm. The guinea pig's ears apparently contain no lysozyme (within the sensi-

Lysozyme Content of Tears

Specimen	Reduction of Optical Density, %
Ring-tailed monkey	99
Human	74
Rhesus monkey	22
Egg-white lysozyme (0γ), control	20
Dogs (range of 8 breeds)	0-15
Guinea pig	0
Egg-white lysozyme (3γ), control	0

tivity of the test), as shown in the Table. Death intervened before the iguana's tears could be tested, but presumably lysozyme would not have been found, judging by the results from the guinea pig.

Alderton, Ward, and Fevold [6] found their egg-white lysozyme to be essentially homogeneous electrophoretically but mentioned the presence of a minor component with a slower mobility. They gave values of 4.49×10^{-5} and 3.7×10^{-5} sq. cm/volt-second, respectively, for the electrophoretic mobility in free electrophoresis of these two components at pH 7.76 and referred to 0 C. These two mobilities give a ratio of 1.21. Tallan and Stein [7] analyzed crystalline-egg-white lysozyme by column chromatography and found three components. Two of these components gave electrophoretic mobilities in free electrophoresis at pH 7.82 and 0.5 C of 4.17×10^{-5} and 3.24×10^{-5} sq. cm/volt-second, yielding a ratio of 1.29. The third component was in a smaller amount and had a lower mobility. Under the conditions reported here, using paper electrophoresis, human-tear lysozyme and crystalline-egg-white lysozyme are identical, giving a single spot the same distance from the origin. This evidently corresponds to the faster-moving component found by the above investigators. The absolute value for electrophoretic mobility calculated from paper electrophoresis data is not comparable to that calculated from free electrophoresis data. The relative rates, however, should be comparable. The ratio of the distances traveled during filter-paper electrophoresis of the human to the animal component

is 1.40. This would indicate that the "slow-moving lysozyme" component of animal tears is probably identifiable with the minor component of Alderton, Ward, and Fevold and with the second component of Tallan and Stein.

Most of the animals, with the possible exceptions of the guinea pig (*h*) and rabbit (*j*), have a fairly high concentration of protein at or near the origin, which is the equivalent position occupied by the γ-globulin of human serum. There seems to be no other protein common to all tears. This would indicate that tears are a true secretion, and that, to a large extent, the proteins are formed *de novo* in the secreting glands.

The following additional specific points may be noted:

(*a*) The desert tortoise seems to have the least number of protein components.

(*h*) The guinea pig is unique in possessing an extremely fast-moving component. It is difficult to keep this component on the paper under these conditions. The dotted line in the Figure indicates that there was buffer interference at the end of the trace which distorted the pattern.

(*i*) The rabbit seems to have a high concentration of albumin, which may be a reflection of the high albumin content of its serum, as shown by Geinitz.[8] This observation may be an exception to the general finding that there is little correlation between plasma proteins and tear proteins.

(*k*) The trace for the dog is representative of the usual pattern given by dog tears. We have found occasional variations from this pattern among different breeds. (Note the range of lysozyme activity in the Table.)

(*m, n, p*) Sheep, goat, and horse tears are fairly similar and are characterized by a component at the origin and a component of greater ionic mobility than that of human albumin.

(*q*) The Himalayan bear tear has the same features as the tears of the sheep, goat, and horse. The bear was especially selected because of the statement in the literature (Walls [4]) that some species of bears are capable of psychic weeping. During the process of obtaining the tear sample the bear cub gave evidence that it was unhappy but no tearing was noted.

(*r*) The elephant has a small pattern, quite reminiscent of the reptiles.

SUMMARY AND CONCLUSION

The tear fluid of some 20 animals has been analyzed by filter-paper electrophoresis. These animals include reptiles, birds, and mammals.

There are great variations in the protein component of tears from animal to animal. A protein component at or near the origin appears to be common to most animal tears.

It appears that several species of animals (mostly among the primates) have a "slow-moving lysozyme" component. Enzymatically this material behaves similarly to, but has only about three-fourths the electrophoretic mobility of, egg-white and human lysozyme.

All the other animal tears tested show no lysozyme within the limits of the test.

The tear fluid appears to be a true secretion. Apparently, unchanged plasma proteins do not contribute significantly to the protein constituents of normal animal tears.

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An Eye with Endothelial Dystrophy and Multiple Malignant Melanomata

Histopathologic Report

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This report concerns a clinical and histopathologic study of an eye containing two apparently independent malignant melanomata and showing, in addition, changes in the cornea consistent with the diagnosis of endothelial dystrophy. A review of the literature indicates the rarity of truly independent multiple malignant tumors in the same eye and reveals surprisingly few histopathologic studies of eyes with endothelial dystrophy. It would seem, therefore, that an eye with both conditions is worth reporting. The eye was made available through the courtesy of Dr. Harold G. Scheie.

REPORT OF CASE

A woman, age 59, was first seen on Aug. 3, 1948, complaining of progressive blurring of vision for five years. Her corrected visual acuity was 6/12—2 O. D. and 6/15+3 O. S. The central portions of both corneas appeared hazy. With the slit lamp, this clouding was found to result from typical changes of endothelial dystrophy with secondary epithelial edema. Although the endothelial changes were more marked in the left eye, secondary bullous edema of the corneal epithelium was more advanced in the right eye. In addition to these corneal findings, a raised pigmented mass was seen within the iris O. S. (Fig. 1), extending from the 11 : 30 to the 12 : 30 o'clock meridian and apparently displacing healthy iris below it, causing a slight flattening of the pupillary border. The tumor completely obliterated the angle from 11 : 30 to 12 : 30 o'clock and extended along the surface of the trabeculum as far as the 2 o'clock meridian. A second, slightly elevated and pigmented lesion, about 3 mm. in diameter, was found on the surface of the left iris between the 8 : 30 and the 9 : 30 o'clock meridian. Although the fundi were not clearly visualized, owing to the corneal haze, no gross lesions were found. Intraocular pressure was found to be 9 mm. Hg (Schiøtz) in each eye.

The patient was observed at intervals for the next five years, during which time the pigmented tumor at the 12 o'clock position became definitely larger and appeared to extend onto the clear cornea from its position deep in the angle. Ocular tension, however, remained normal. On Sept. 14, 1953, she was seen by Dr. George Kelly and by Dr. Algernon Reese, who agreed that the larger lesion was probably a malignant melanoma and that the flat lesion, nasally, was relatively benign. Enucleation was therefore recommended and carried out on Sept. 16. General physical examination just prior to enucleation was entirely negative and revealed no evidence of tumor other than those already described in the eye.

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From the Department of Ophthalmology, Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia.

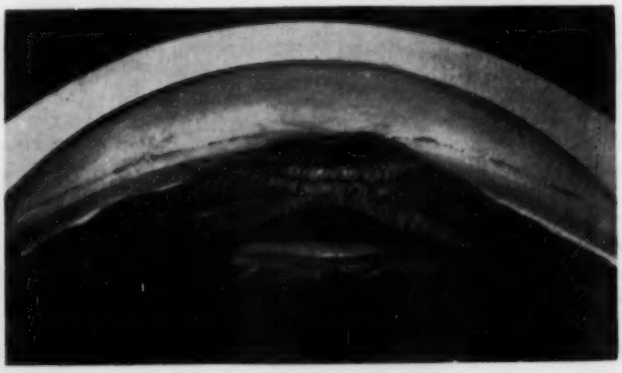
Fig. 1.—Appearance of the left eye before enucleation, showing the malignant and solid tumor, above, and the flat, benign lesion, nasally.

Gross Examination.—The globe measured 23×23×24 mm. It was sectioned vertically, so that the central block contained the tumor in the 12 o'clock meridian. The nasal calotte, containing the flat pigmented tumor on the surface of the iris, was also embedded and sectioned serially. A third, slightly elevated and deeply pigmented, tumor, about 3 mm. in diameter, which had not been noted clinically, was discovered within the choroid in the inferior temporal quadrant of the eye.

Microscopic Examination.—The corneal epithelium was separated at intervals from Bowman's membrane by a clear eosinophilic coagulum forming numerous small blebs. The corneal stroma was normal. Descemet's membrane (Fig. 2) was irregularly thickened, and its entire posterior surface was covered by nodular excrescences, which were more numerous and larger in the peripheral portions. The endothelium was absent over some of these nodules, and remaining endothelial cells were elongated and cystic. Pigment granules were frequently found within and adjacent to them. With a variety of connective tissue stains, the excrescences appeared to have staining properties identical with those of Descemet's membrane.

The large tumor at the root of the iris in the 12 o'clock meridian extended posteriorly to include most of the ciliary body and anteriorly to obliterate the angle (Fig. 3). It was heavily

Fig. 2.—Gonioscopic appearance of the larger tumor at the 12 o'clock meridian.



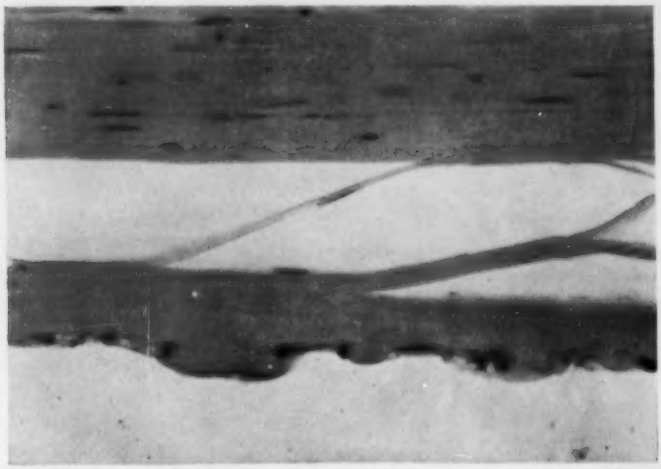


Fig. 3.—Section through the central portion of the cornea, showing irregular thickening and nodular excrescences of Descemet's membrane. The endothelial cells are degenerative. Reduced to ⅝ of mag. × 570.

pigmented in some portions and was composed of spindle cells, most of which contained prominent nucleoli. The tumor was classified as a malignant melanoma, spindle-cell Type B. Wilder reticulin stains revealed a relatively small amount of reticulin. Serial sections made through the smaller iris lesion, in the nasal calotte, showed no evidence of a solid tumor. In some areas, however, several layers of pigmented spindle-shaped cells on the anterior surface of the iris were thought to be characteristic of a benign iris melanoma (Fig. 4).

The choroid was normal except in the area in the inferior temporal quadrant containing the small melanotic tumor discovered at the time of gross examination. This tumor appeared grossly to be composed of two distinct layers (Fig. 5). The more peripheral layer, which was sparsely pigmented, was a segment of the long ciliary nerve. Internal to the nerve was a

Fig. 4.—Section of the entire globe, showing the malignant melanoma of the ciliary body. Reduced to ⅜ of mag. × 5.

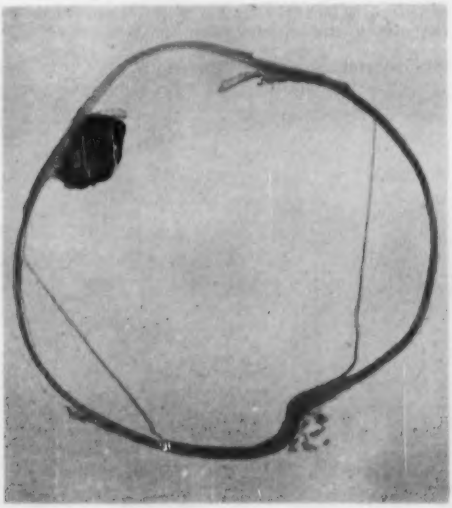


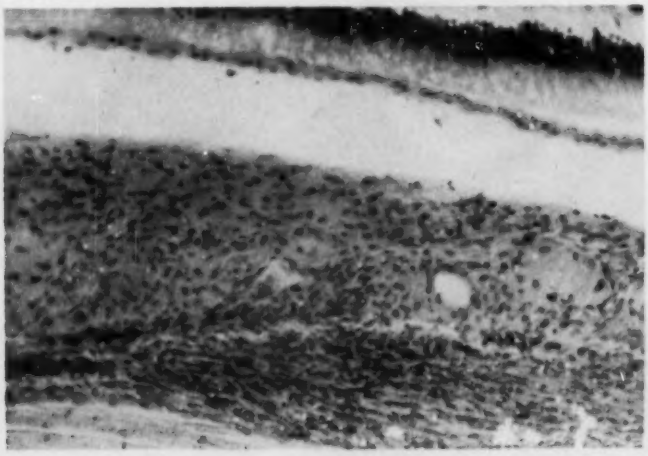
Fig. 5.—Section through the choroidal malignant melanoma, illustrating its origin from the long ciliary nerve. Reduced to ⅘ of mag. × 38.

second layer, composed of large, heavily pigmented cells with abundant cytoplasm arranged in small oval clusters (Fig. 6). These cells closely resembled the epithelioid type of malignant melanoma cells. There were early cystic changes in the outer layers of the retina overlying this tumor. The remaining retina was normal. The optic nerve showed no cupping or atrophy. The sclera and adnexa were normal.

COMMENT

The simultaneous occurrence of more than one malignant melanoma in the same eye has been considered extremely unusual. Reese [1] was able to find no authentic report of multiple primary tumors in which he felt that the criteria for independent tumor growth had been fulfilled. Rosen and Moulton,[2] however, have since reported an eye with at least six apparently independent malignant melanomata in the choroid and ciliary body. In their review of the literature they found only

Fig. 6.—High-power view of a bleached section of the choroidal melanoma. The segment of the long ciliary nerve is shown in the lower segment of the picture.



two previous reports of eyes which may have contained multiple primary tumors, although the studies of these eyes were not conclusive.

In the eye reported here, serial sections made through the smaller choroidal tumor revealed no connection with that of the ciliary body. The two tumors, both of which were thought to be malignant, were of different cell types, suggesting, at least, a separate origin. The smaller of the tumors appeared clearly to originate in the long ciliary nerve, and it would seem unlikely that the much larger tumor in the ciliary body could have arisen from it by seeding or by metastatic extension.

It is now almost universally agreed that the epithelial dystrophy of the cornea described by Fuchs [3] in 1910 is a late manifestation of degenerative changes originating in the endothelium. Although some patients with endothelial dystrophy do not develop epithelial edema during their lifetime, there seems to be little justification for a separate classification of the two conditions. Earlier writers (Koeppe [4]; Kraupa [5]) had suspected an endothelial defect in eyes with epithelial dystrophy, but the first clinical description of the nature of these endothelial changes was made by Vogt [6] in 1921. Because of the development of the method of examination by specular reflection, Vogt was able to predict with reasonable accuracy the pathologic morphology of the disease. He made no report of histopathologic studies of endothelial dystrophy, however, until 1930.[7] Although large numbers of clinical observations have been made subsequently, a review of the literature reveals histopathologic reports of only eight eyes with the condition.

Early pathologic reports by Vogt, Goar,[8] and von Hippel [9] described degenerative changes in the endothelium coupled with nodular excrescences of Descemet's membrane. These findings have been verified more recently by Calhoun [10] and Stocker.[11] Verhoeff,* in 1944, reported the histologic study of an eye with endothelial dystrophy in which there was reduplication of Descemet's membrane and partial absence of endothelium, but in this eye there were no nodular excrescences. Stocker [12] reported a similar absence of excrescences in an eye with endothelial and epithelial dystrophy.

The term cornea guttata is used to describe the drop-like excrescences of Descemet's membrane often associated with endothelial dystrophy. Wart-like excrescences in the peripheral portions of Descemet's membrane are very common in normal eyes of older people, and many authors believe that cornea guttata is simply the result of axial extension of these peripheral nodules. Von der Heydt,† Goar, Stocker, and others, however, have pointed out that in most instances cornea guttata begins centrally and spreads to the periphery, and represents a separate entity.

The mechanism producing reduplication and the formation of excrescences of Descemet's membrane is not thoroughly understood. Most authors agree with Verhoeff,‡ who stated that these phenomena are the result of secretion by hyperplastic or abiotrophic endothelium. Epithelial changes are produced when subsequent degeneration of endothelial cells allows fluid to enter the cornea.

SUMMARY

A histopathologic report of an eye with endothelial dystrophy and multiple independent melanomata is made. A review of the literature indicates the infrequent

* Verhoeff, F. H., quoted by Lloyd.[12]

† von der Heydt, R., in discussion on paper by Goar.[8]

‡ Verhoeff, F. H., in discussion on paper by Levitt and Lloyd.[14]

occurrence of multiple malignant melanomata in the same eye and the relative infrequency of histologic reports of endothelial dystrophy. The two melanotic tumors, both of which were interpreted as malignant melanomata, seem to fulfill the criteria for independent tumor growth.

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Glucose Utilization of the Retina

IV. Influence of Toxic Substances and Enzyme Inhibitors

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Since carbohydrates are the main source of energy of the retina, it was thought that the glucose uptake of the retina might be an indicator of chemical damage to the retinal metabolism.

This report deals with the influence on the glucose uptake of the retina of some substances which are known to cause toxic amblyopia (methyl alcohol, quinine, arsenicals) and of compounds which damage the visual cells (iodoacetic acid, sodium iodate). Because of the close relationship of the carbohydrate metabolism to the resynthesis of acetylcholine, it was thought that cholinesterase inhibitors might influence the glucose uptake of the retina. Therefore the effects of physostigmine and isoflurophate (DFP; diisopropyl fluorophosphate) were investigated. Since a high concentration of carbonic anhydrase is present in the retina,[1] the influence of the carbonic anhydrase inhibitor acetazoleamide (Diamox) was tested. The effects of ethionine, a competitive antagonist of methionine, and of the folic acid antagonist Aminopterin (4-aminopteroyl glutamic acid) were also studied.

The effects on glucose utilization of the retina of various media, and of various physiological and dietary conditions, hormones, and endocrine deficiencies have been described in previous papers.*

MATERIALS AND METHODS

Albino male rats weighing 90-120 gm. were employed in all experiments. The technique for the determination of the glucose utilization of the retina was described in detail in a previous paper.[2] In cases where the glucose utilization of the retina and that of the brain were determined simultaneously in the same animal the brain was removed first. It was immediately put into an isotonic saline solution cooled on ice. A slice of the cerebral cortex, 0.5 mm. thick, was transferred into Krebs-Ringer bicarbonate solution containing 200 mg. per 100 cc. of glucose and incubated for two and a half hours in the same way as the retina. It was then removed, washed in distilled water, dried for 30 minutes at 100 C, and weighed.

In cases where the glucose utilization of the retina and that of the diaphragm of the same animal were examined, the diaphragm was removed in toto before enucleation and treated in the same way as the brain slice.

RESULTS

The details for all the experiments are summarized in Tables 1 to 4.

The results for retinal tissue are expressed as milligrams of glucose uptake per retina. Where the glucose utilization of the retina was compared with that of brain

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From the Department of Ophthalmology, Rothschild-Hadassah-University Hospital, and the Department of Pathological Physiology of the Hebrew University Medical School.
* References 2-4.

TABLE 1.—*Influence of Substances Causing Toxic Amblyopia on Glucose Utilization of Retina*

Substance	Dose	Route of Administration	Length of Time	Medium	Experimental		Control	
					No. of Animals	Glucose Uptake of Retina, Mg.	No. of Animals	Glucose Uptake of Retina, Mg.
Methyl alcohol	800 mg./100 gm.	Intraperitoneal	1½ hr.	Homologous serum	5	0.51±0.04	12	0.62±0.036
Methyl alcohol	800 mg./100 gm.	Intraperitoneal	2½ hr.		8	0.65±0.03	..	.....
Methyl alcohol	800 mg./100 gm.	Intraperitoneal	24 hr.		5	0.53±0.04	..	.....
Methyl alcohol	800 mg./100 gm.	Intraperitoneal	15 days		3	0.61	..	.....
Methyl alcohol	800 mg./100 gm.	Intraperitoneal	2½ hr.	Krebs-Ringer bicarbonate solution	4	0.43	3	0.98
Methyl alcohol	950 mg./100 gm.	Oral	5 hr.	Homologous serum	3	0.63	3	0.62
Methyl alcohol	950 mg./100 gm.	Oral	18 hr.		3	0.49	2	0.52
Formaldehyde	20 mg./100 gm.*	Intraperitoneal	2½ hr.	Autologous serum	11	0.55±0.02	9	0.54±0.02
Ammonium chloride	50 mg./100 gm.†	Intraperitoneal	4 hr.	Autologous serum	35	0.61±0.02	28	0.68±0.02
Sodium acetoacetate	100 mg.	In vitro	.....	Krebs-Ringer phosphate solution	12	0.27±0.02	11	0.30±0.01
Quinine hydrochloride	30 mg./100 gm.‡	Subcutaneous	10 days	Homologous serum	4	0.58±0.03	3	0.57
Sodium cacodylate	50 mg./100 gm.	Intraperitoneal	3 days	Autologous serum	2	0.52	2	0.52

* 10 mg./100 gm. followed by two injections of 5 mg. at a 30-minute interval.
† Two injections of 5% ammonium chloride (25 mg./100 gm. each) 30 minutes apart.
‡ 3 mg./100 gm. daily for 10 days.

TABLE 2.—*Influence of Inhibitors of Cholinesterase and Carbonic Anhydrase on Glucose Utilization of Retina*

Substance	Dose	Route of Administration	Length of Time	Medium	Experimental		Control	
					No. of Animals	Glucose Uptake of Retina, Mg.	No. of Animals	Glucose Uptake of Retina, Mg.
Physostigmine	50 gm./100 gm.	Subcutaneous	45 min.	Autologous serum	2	0.65	2	0.65
	75 gm./100 gm.	Subcutaneous	45 min.	Autologous serum	2	0.60	2	0.57
Isoflurophate	0.24 mg./100 gm.	Subcutaneous	20 min.	Autologous serum	3	0.56	3	0.61
	1.00 mg./100 gm.	Subcutaneous	2 hr.	Autologous serum	2	0.66	2	0.57
Acetazoleamide	150 mg./100 gm.	Subcutaneous	2 hr.	Autologous serum	2	0.62	2	0.66

TABLE 3.—*Influence of Methionine and Folic Acid Antagonists on Glucose Uptake of Retina*

Substance	Dose	Route of Administration	Length of Time	Medium	Experimental		Control	
					No. of Animals	Glucose Uptake of Retina, Mg.	No. of Animals	Glucose Uptake of Retina, Mg.
Ethionine	0.23 gm./100 gm.	Subcutaneous	24 hr.	Autologous serum	6	0.62±0.05	6	0.63±0.05
Aminopterin	0.12 mg./100 gm.*	Oral	4 days	Homologous serum	6	0.60±0.02	2	0.64

* Mixed food 0.4 mg./100 gm.

and diaphragm, the results for all three tissues are expressed as milligrams of glucose uptake per 10 mg. dry weight of tissue.

None of the substances tested, except iodoacetic acid, inhibited glucose uptake. Iodoacetic acid inhibited by 30% the glucose utilization of the retina without affecting the glucose uptake of the brain and diaphragm.

The oxygen uptake of the retinae of six rats poisoned by intraperitoneal injection of methyl alcohol was measured but did not deviate from the normal (six experiments—QO_2 9.0±0.7 μl/mg. dry weight/hour; six controls—QO_2 9.9±1.0 μl/mg. dry weight/hour.

The rats which received methyl alcohol 800 mg/100 gm. intraperitoneally were in deep narcosis for about three hours. About 30% of the animals died within 30 minutes. Homologous, instead of autologous, serum had to be used in these experiments, since not enough blood could be obtained from the deeply shocked animals. The rats which were given methyl alcohol 950 mg/100 gm. by stomach tube did not show any systemic reactions except for some spastic movements. The rats injected with formaldehyde did not show untoward effects, and none of the animals died after the injection.

The acidosis caused by intraperitoneal injection of 5% ammonium chloride (25 mg/100 gm.) led to a fall in carbon dioxide-combining power of the plasma to 20-28 vol. % over a period of four hours.

The rats injected with quinine intramuscularly showed necrotic ulcers at the sites of injection.

Ethionine was injected subcutaneously into rats which had been fasted for 12 hours. Twenty-four hours later, when the animals were killed, all were found to have fatty infiltration of the liver.

Rats fed Aminopterin had lost about 30% of their original body weight when they were killed, after four days.

COMMENT

The problem of methanol poisoning is still unsettled as regards the actual toxic agent, the toxic mechanism, and the anatomical site primarily affected. One of the main difficulties in answering the various questions arises from the fact that experimental animals do not respond to methanol intoxication in the same way as does man.[5] Oguchi [6] found that poisons which injure vision, such as methyl alcohol, quinine, and illuminating gas, reduce the oxygen consumption of the retina of frogs and rats by 25%-50%. Our experiments, in which the oxygen uptake did not change, are in contradiction to these findings. We found that the glucose uptake as well was unaffected by methyl alcohol.

In recent years formaldehyde, a direct oxidation product of methanol, has been thought to be the toxic agent in methanol poisoning. Potts and Johnson [7] studied the inhibitory effect of methanol, formaldehyde, and formate in vitro on a number of enzyme reactions on surviving beef retina. The enzyme process most sensitive to formaldehyde inhibition was glycolysis. However, in our experiments in which formaldehyde was injected in vivo the glucose uptake of the excised retina remained unaltered. These were massive doses of 20 mg/100 gm., as compared with the L. $D._{50}$ of 70 mg/kg. found by Gilger and associates [8] for mice.

Severe acidosis is necessary for, and parallels the development to, amblyopia and amaurosis.† It was therefore interesting to investigate whether acidosis would influence the glucose uptake of the retina. Though the carbon dioxide-combining

† References 5 and 9.

TABLE 4.—*Influence of Substances Causing Damage to Visual Cells and/or Pig*

Material	Dose	Route of Administration	Length of Time	Medium
Iodoacetic acid	4.8 mg./100 gm.	Intravenous	2 hr.	Krebs-Ringer bicarbonate solution
Sodium iodate	10 mg./100 gm.	Intravenous	2 hr.	Krebs-Ringer bicarbonate solution
	20 mg./100 gm.	Intravenous	2 hr.	Krebs-Ringer bicarbonate solution
	15 mg./100 gm.	Intravenous	24 hr.	Krebs-Ringer bicarbonate solution
Azide	2 mg./100 gm.	Intravenous	30 min.	Autologous serum

power of the blood in our rats was lowered to 20-28 vol. % for a period of four hours, no effect on the glucose utilization of the retina or diaphragm ‡ was noticed.

In connection with acidosis, it seemed of interest to study the influence of acetoacetate on the carbohydrate metabolism of the retina. Chari and Wertheimer [10] found that diaphragm of rats incubated with acetoacetate showed increased glucose utilization. No such effect was observed in the retina of rats.

Acetylcholine, which is involved in the transmission of nerve impulses, is present in the retina. Its amount is controlled by the enzyme cholinesterase, which is found in great concentrations in the synaptic layers of the retina. However, the potent cholinesterase inhibitors physostigmine and isoflurophate, when given in doses 50-60 times the average human dose, had no effect on the glucose utilization of the retina.

It has been assumed that tissues with strong aerobic glycolytic activity and with a poorly developed vasculature, such as the retina, need their high concentration of carbonic anhydrase in order to catalyze the rapid dissociation of carbonic acid into water and carbon dioxide. Nevertheless, 400 times the comparable dose of acetazoleamide for man did not influence the glucose uptake of the retina.

Of all the substances tested, only iodoacetic acid reduced the glucose uptake of the retina, but it did not influence the glucose utilization of the brain and diaphragm. Noell [11] showed that iodoacetic acid abolished vision and the electrical reaction of the optic tract to illumination within a few minutes after intravenous injection and selectively damaged the visual cells. He assumed that iodoacetic acid caused inhibition of glycolysis in the visual cells. Such inhibitions of retinal glycolysis by iodoacetic acid was demonstrated in vitro by previous workers.§

Sodium iodate in large doses damages the pigment epithelium of the retina and the outer limbs of the visual cells. However, it did not affect the glucose uptake of the retina in our rats. The doses used were two to four times as high as the ones that caused marked retinal pigmentary degeneration in rabbits (Sorsby [14]).

Azide was found by Noell [11] to increase the potential difference across the eye. This effect was supposed to be produced by interference with electrochemical processes at the boundaries between retina and choroid. Intravenous injections of azide in rats did not alter the normal glucose utilization of the retina.

SUMMARY

The influence of methyl alcohol, quinine, and sodium cacodylate on the glucose uptake of the retina of rats was investigated. None of these substances, nor formal-

‡ Yardeni-Yaron, E.: Personal communication.

§ References 12 and 13.

ment Epithelium of the Retina on Glucose Uptake of Retina, Brain, and Diaphragm

Retina				Brain				Diaphragm			
Experimental		Control		Experimental		Control		Experimental		Control	
No. of Animals	Mg. Glucose/ 10 Mg. Dry Weight	No. of Animals	Mg. Glucose/ 10 Mg. Dry Weight	No. of Animals	Mg. Glucose/ 10 Mg. Dry Weight	No. of Animals	Mg. Glucose/ 10 Mg. Dry Weight	No. of Animals	Mg. Glucose/ 10 Mg. Dry Weight	No. of Animals	Mg. Glucose/ 10 Mg. Dry Weight
29	2.25±0.13	27	3.25±0.18	21	0.80±0.02	19	0.77±0.02	19	0.80±0.02	17	0.81±0.03
3	3.00	2	3.30	4	0.92	2	0.71	..	.....	..	.....
3	2.80	2	3.00	3	0.90	2	1.06	..	.....	..	.....
5	2.6	2	2.9	4	0.86	2	0.92	..	.....	..	.....
5	3.9±0.3	5	3.7±0.3	..	.....	..	.....	..	.....	..	.....

dehyde, an oxidation product of methyl alcohol, nor acidosis, thought to be necessary for the development of amaurosis in methyl alcohol poisoning, had any influence on the normal glucose utilization of the retina.

Iodoacetic acid caused a 30% inhibition of the glucose uptake of the retina, but the glucose utilization of the brain and diaphragm was not affected.

Physostigmine, isoflurophate (DFP), acetazoleamide (Diamox), ethionine, and Aminopterin (4-aminopteroyl glutamic acid) had no effect on the glucose utilization of the retina.

No change in the glucose uptake of the retina was caused by intravenous injections of sodium iodate or azide.

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A Method of Cataract Extraction Following Filtering Operations for Glaucoma

Perpendicular Corneal Incision Anterior to the Cicatrix

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For several reasons, the prognosis should be guarded in cataract extraction following previous filtering operations for glaucoma. Such eyes may show varying degrees of visual loss from the glaucomatous process itself which preoperative tests for retinal function are not sufficiently sensitive to detect. Degenerative changes may have occurred in the ocular tissues that make the response of the eye to the trauma of surgery unpredictable. Fluid vitreous is commoner with added frequency of vitreous loss and attendant complications. The iris may show severe atrophy. The anterior chamber may be so shallow that operation is difficult. Sequelae of glaucoma surgery may greatly complicate cataract extraction and interfere with the final visual results. For example, extensive adhesions of the iris to the lens or cornea may have occurred. If the iris has been adherent to the cornea, there is predisposition to postoperative corneal edema and opacification, due to defects in the endothelium. Posterior synechia must be freed prior to intracapsular extraction. Iridencleisis and, less often, corneoscleral trephination may have resulted in an updrawn pupil. Unless the position of the pupil is corrected at the time of the cataract extraction, it may become aggravated and the pupillary opening completely occluded following operation. The problem of incision is of great importance because of the danger of postoperative rise in ocular tension from obliteration of the filtering cicatrix. Also, difficulties may be encountered in making an incision due to distortion of the angle by the filtration procedure or because of a shallow chamber. Delayed re-formation of the anterior chamber following extraction is to be feared.

Considerable difference of opinion is found in the literature regarding the best site for making the incision for cataract extraction following filtering operations for glaucoma. The following locations have been suggested: (1) superiorly through the filtering area; (2) superiorly through clear cornea anterior to the filtering area; (3) laterally, inferolaterally, or directly inferiorly at the limbus, completely avoiding the filtering area.

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Each location has advocates, as pointed out by Callahan [1] and Rizzuti [2] in excellent reviews. Buffington,[3] Judd,* Weekers and associates,[4] and Snip † advocated making the section superiorly through the filtration area. McLean,[5] Gasteiger,[6] and Pillat [7] suggested making the section anterior to the bleb, while Kirby [8] and Guyton [9] did so only if the tension was normal. If hypotony was present, they advised the section through the bleb. Van der Straeten,[10] Castroviejo,‡ Gifford,[11] and Labib [12] suggested a temporal approach, and Callahan [1] made his section inferiorly and temporally at the limbus away from the filtering area. Williamson-Noble,[13] in a recent article, advocated section through the filtering area. Castroviejo,‡ Spaeth,[14] and Rizzuti [2] have utilized an inferior approach.

Advantages and disadvantages can be cited for all of these methods. Incision through the bleb is easiest and permits use of conventional technique. The consensus, however, is that this method is accompanied by postoperative rise of pressure more frequently than are other methods, owing to failure of filtration. Conventional incisions placed within clear cornea anterior to the filtration area increase the difficulty of delivery of the lens because of a large overhanging ledge of cornea. Inferior and inferotemporal incisions are somewhat more difficult to execute because of their location. Technique practiced every day must be reversed, and instrumentation is somewhat more difficult. Delivery of the lens through an inferior incision is particularly difficult following iridencleisis, where the pupil tends to be updrawn. Removal of the lens through such a pupil, with the sphincter under some tension, is not easy. In addition, the iris, usually, must be mutilated further by doing one or more peripheral iridectomies inferiorly to diminish the hazard of peripheral anterior synechia and iris prolapse. In my opinion, this approach should be reserved for use after corneoscleral trephination when a round pupil has been preserved, in which case delivery of the lens is not difficult and a nearly intact iris is present.

My method, presented in this paper, consists of an incision in clear cornea, anterior to the filtration area, made perpendicular to the surface of the cornea. Direct appositional sutures are used, which are inserted through the cut edges of clear cornea anterior to the filtering cicatrix. This type of incision leaves the filtration area undisturbed. Because it is made perpendicularly to the surface of the cornea just within the limbus, the overhanging ledge of cornea found after beveled incision is eliminated and delivery of the lens is facilitated (Fig. 1). The use of such an incision also was suggested because delayed re-formation of the anterior chamber and choroidal detachment are extremely rare following keratoplasty. The explanation may be a mechanical one, based on the superiority of this type of incision and wound closure, or may be inherent in the tissues, for it is my experience that corneal wounds heal more readily than scleral wounds. It does seem mechanically reasonable, however, that when direct appositional sutures are used to close perpendicular edges, the tissues become still more firmly approximated as postoperative edema involves the wound lips. The tissues can expand only along the line of the sutures, so that the lines of force more firmly close the wound (Fig. 2). Castroviejo ‡ employs a perpendicular incision made at the limbus beneath a limbus-based conjunctival flap for uncomplicated cataract extractions.

* Judd, J. H., in discussion on article by Guyton.[9]

† Snip, R. T.: Cataract Extraction Following Filtering Operation, Wilmer Residents Association program, 1949.

‡ Castroviejo, R.: Personal communication to the author.

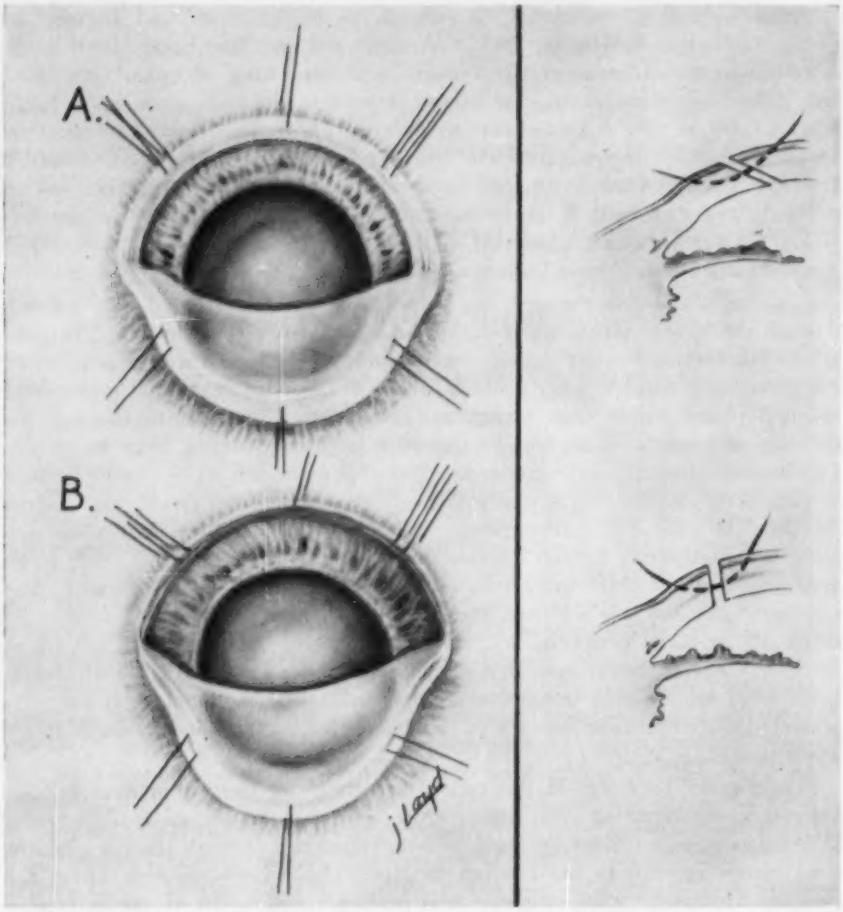
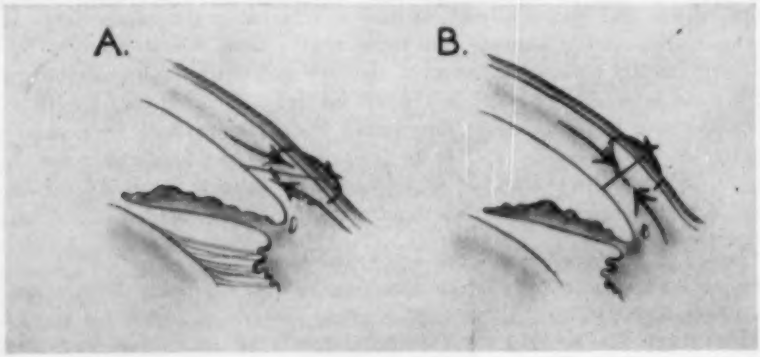


Fig. 1.—*A*, large corneal ledge after beveled incision. *B*, small corneal ledge remaining after perpendicular corneal incision.

Fig. 2.—*A*, lines of force along sutures tend to cause wound edges to override, with swelling of tissue following beveled incision. *B*, lines of force along sutures tend to seal wound more firmly, with swelling of tissues following perpendicular incision.



TECHNIQUE

The operation can be done with local or general anesthesia and adequate akinesia. A superior rectus suture is used. The eye is fixed with a scleral pick (Fig. 3). A partially penetrating scratch incision is made perpendicular to the surface of the cornea, about 3 mm. long and 1 mm. within the limbus at the 12 : 30 to 2 : 00 and 10 : 00 to 11 : 30 o'clock meridians. A double-armed mattress suture is placed across the grooves toward the upper limbus, emerging through clear cornea (Fig. 4). Grieshaber needles with 000000 nonabsorbable surgical (silk) sutures, or Grieshaber-type Ethicon needles with 000000 nonabsorbable (silk) or absorbable surgical sutures are the best for this purpose. The sutures are then picked up in the groove by using a Wiener scleral hook and the loops pulled out (Fig. 5). The loops are retracted in the following way: A small hemostat is passed through the upper arms of the loops and clamped to a drape, with the free ends of the suture placed so that the hemostat rests upon them (Fig. 6). The loops of the suture are not clamped in the hemostat, but only rest beneath the tip, which is attached to the drape

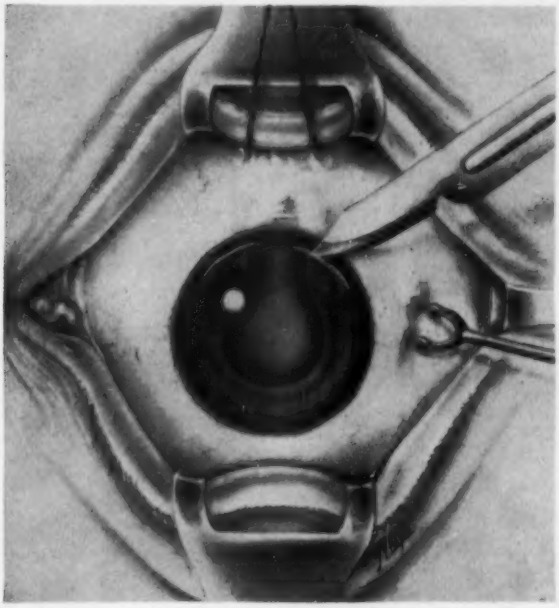


Fig. 3. — Eye fixed with scleral pick. Partially penetrating scratch incisions made perpendicularly into clear cornea, upper nasal and temporal quadrants.

near the middle of the eyebrow. The hemostat then serves by its weight to retain the upper arms of the loop and to hold the loose ends of the suture, so that an assistant or the operator need only retract the lower arms. The anterior chamber is entered by inserting a keratome with the tip inverted or a knife needle between the arms of the temporal loops (Fig. 7). If the chamber is very shallow, the initial incision can be made with a knife needle inserted obliquely or by scratching with the tip of a keratome to help ensure against laceration of the lens capsule. Entering the chamber over the intact iris away from the iris coloboma also helps to avoid injury to the lens capsule. The chamber should be entered temporally because an opening in this location is more easily enlarged with a scissors than one made nasally, since there is no interference by the bridge of the nose. The blade of a scissors is introduced and the incision is enlarged nasally, great care being taken to avoid injury to the lens capsule over the area of the coloboma (Fig. 8). The scissors are held to cut perpendicularly to the surface of the cornea. When the incision has been extended just beyond the 12 o'clock meridian, another single-arm interrupted suture should be placed at 12 o'clock for further wound support. The incision is then enlarged nasally between the two loops of the nasal suture, which are retracted. At least a half-section usually is necessary to provide room for delivery of the lens because the incision is placed within the limbus. When the incision has been completed, the loops of the suture are shortened until

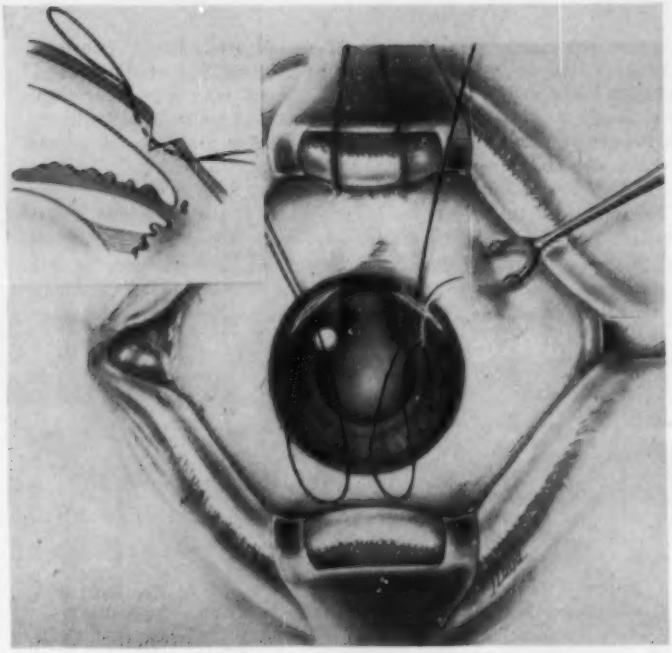


Fig. 4.—Double-armed mattress sutures inserted across partially penetrating corneal incisions.

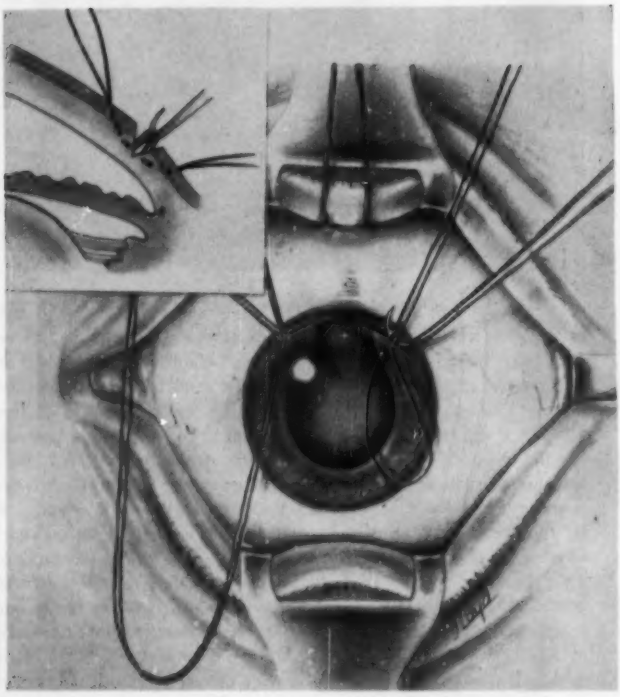


Fig. 5.—Sutures picked up and withdrawn from corneal incision by scleral hook.

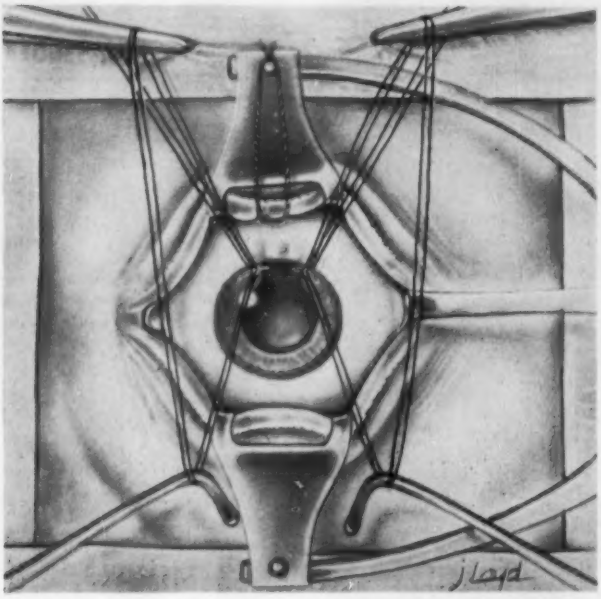


Fig. 6.—Loops of suture retracted superiorly by mosquito hemostat attached to drape and inferiorly by muscle hook.

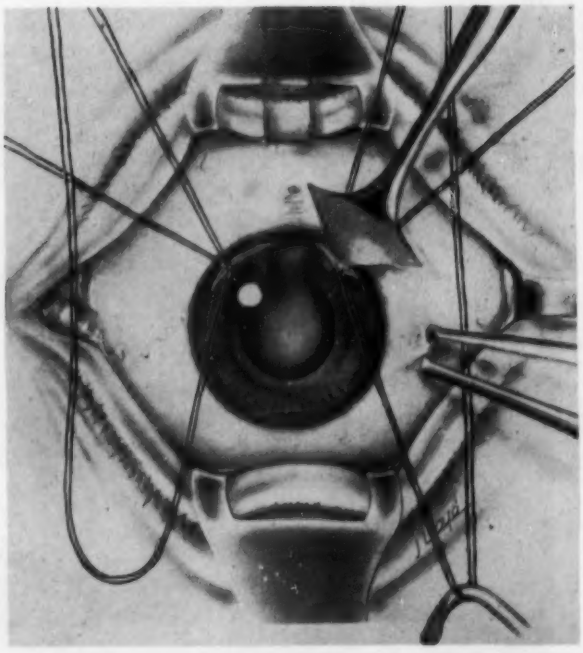


Fig. 7.—Penetrating incision into anterior chamber temporally is made with inverted keratome to ensure perpendicular incision.

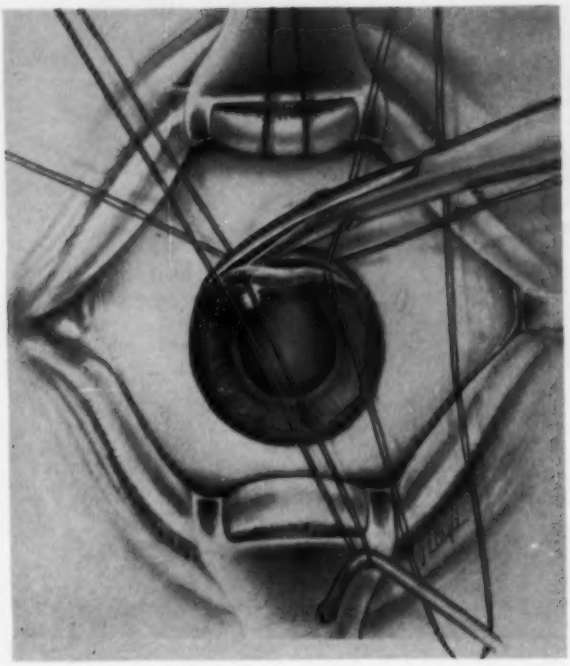


Fig. 8.—Keratome incision enlarged nasally with scissors cutting perpendicular to the surface of the cornea.

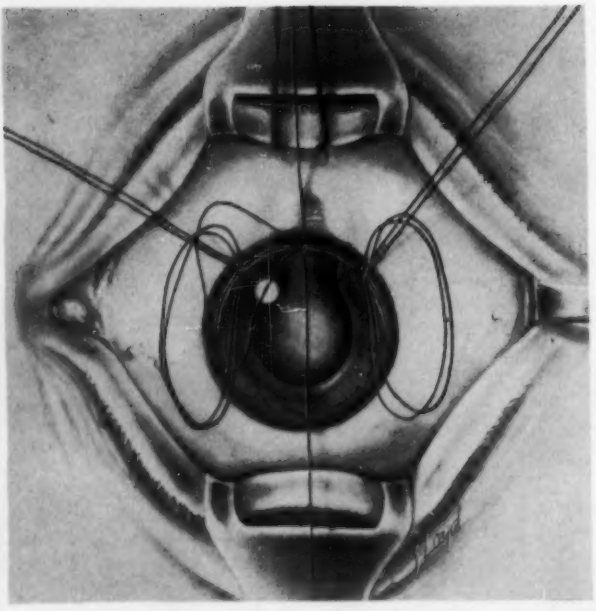


Fig. 9.—Incision enlarged and loops prepared for delivery of lens.

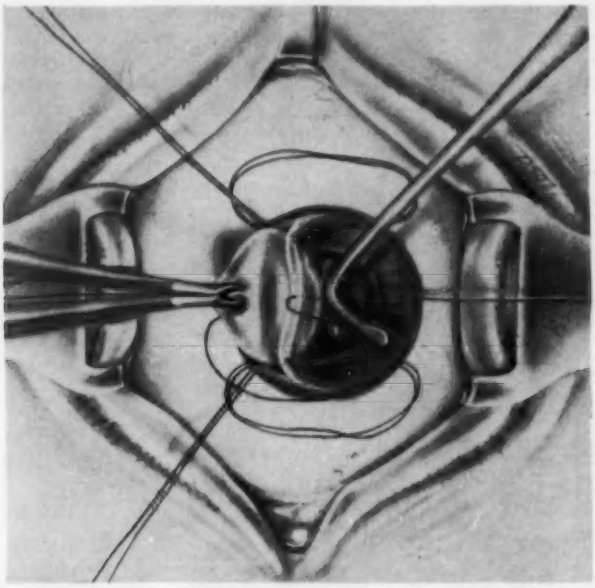


Fig. 10.—Extraction of lens by tumbling method. Loops of sutures do not interfere.

only long enough to permit delivery of the lens. They are then placed downward toward the lower limits of the incision (Fig. 9). The loop of the 12-o'clock suture must be slightly longer than the nasal and temporal sutures. The mattress type of suture diverted upward, as pointed out by Derby,[18] permits rapid wound closure with little tendency to gape while the sutures are being tightened. The lens is delivered, using the operator's method of choice (Fig. 10). Prior to the delivery of the lens care must be taken to free posterior synechia, which occurs especially

Fig. 11.—Photograph of eye showing effect of sphincterotomy done at time of cataract extraction to correct updrawn pupil following iridencleisis.

Results of Cataract Extraction Following Filtering Operation for Glaucoma

Eye	Age	Type of Glaucoma	Glaucoma Operation	Intracapsular Cataract Extraction	Complications		Postoperative Refraction & Visual Acuity	Post-operative Tension, Mm. Hg (Schiøtz)
					Operative	Postoperative		
1	67	Chronic simple	Iridencleisis 1950	3/21/51	.....	.....	+10.00⊂+2.50x175=6/18; optic atrophy	27
2	67	Chronic simple	Iridencleisis 1950	5/ 2/51	.....	Severe irido-cyclitis	+11.00⊂+1.50x20=6/12; optic atrophy	24
3	70	Chronic simple	Corneoscleral trephination 1951	10/ 1/53	Vitreous loss	Updrawn pupil —iridocapsu-lotomy 2/25/54	+18.00⊂+1.50x90=6/15; optic atrophy	17
4	71	Chronic simple	Iridencleisis 6/24/53	10/22/53	.....	.....	+11.00⊂+3.00x180=6/150; optic atrophy	17
5	68	Chronic simple	Corneoscleral trephination 1946	11/12/53	.....	.....	+15.00⊂+0.50x100=6/9	17
6	64	Chronic simple	Iridencleisis 1952	1/ 7/54	Vitreous loss	.....	+15.00⊂+0.50x100=6/9; optic atrophy	20
7	68	Chronic simple	Corneoscleral trephination 1946	3/ 4/54	.....	.....	+14.00⊂+1.25x180=6/9; central choroiditis	20
8	83	Chronic simple	Corneoscleral trephination 1950	2/ 4/54	.....	.....	+12.25⊂+1.25x150=6/6	20
9	69	Chronic simple	Corneoscleral trephination 1946	5/20/54	.....	.....	+10.00⊂+1.50x30=6/60; central choroiditis	24
10	76	Chronic narrow-angle	Iridencleisis 1950	5/20/54	.....	.....	+15.00⊂+1.50x145=6/9	13
11	62	Chronic simple	Iridencleisis 1950	10/22/54	.....	Emptied chamber 10th day	+9.00⊂+1.00x180=6/9	22
12	71	Chronic simple	Iridencleisis with sclerectomy 1954	10/29/54	.....	.....	+11.00⊂+1.00x65=6/9; optic atrophy	20
13	71	Chronic simple	Iridencleisis with sclerectomy 1954	3/31/55	.....	Emptied chamber 11th day	+10.50⊂+1.00x100=6/6	24
14 *	82	Chronic simple	Corneoscleral trephination 1940	5/17/55	.....	.....	+11.00⊂+1.00x130=6/12; optic atrophy	22
15	69	Chronic narrow-angle	Iridencleisis 1952	6/14/55	.....	.....	+15.00⊂+1.00x135=6/6	22
16	64	Chronic simple	Iridencleisis 1953	6/14/55	.....	.....	+9.00⊂+3.25x90=6/60; optic atrophy	17
17	64	Chronic simple	Iridencleisis 1953	6/27/55	.....	.....	+11.00⊂+1.50x140=6/15; optic atrophy	20
18	64	Chronic simple	Iridencleisis 1950	9/15/55	.....	Choroidal detach-ment	+13.00=6/60; optic atrophy	20
19	64	Chronic simple	Iridencleisis 1950	9/24/55	.....	.....	+11.00⊂+2.00x135=6/7.5	24
20	64	Chronic simple	Iridencleisis 1947	10/27/55	.....	.....	+14.50⊂+1.00x150=6/7.5	15
21	75	Chronic simple	Corneoscleral trephination 1948	11/ 3/55	.....	.....	+11.50⊂+2.00x5=6/12; optic atrophy	17
22	64	Chronic simple	Iridencleisis 1950	12/ 1/55	.....	.....	+12.50⊂+0.50x142½=6/6	17

* Patient 14 has had an elevation in ocular tension up to 35 mm. Hg (Schiøtz) since this paper was submitted.

after iridencleisis. If the pupil has appeared updrawn preoperatively, a sphincterotomy is indicated at 6 o'clock. This not only facilitates delivery of the lens but prevents an updrawn pupil postoperatively (Fig. 11). After delivery of the lens, the sutures are pulled up and tied (Fig. 12). If any tendency toward gaping of the wound is found, further interrupted sutures can easily be placed. The sutures are left in place for 10 days to 2 weeks prior to removal. Only the eye operated on is bandaged. Postoperative care is conventional.

PRESENTATION OF CASES

Cataract extractions, employing a perpendicular corneal incision, were done on 22 eyes that had had previous filtering operations for glaucoma (Table). Twenty eyes had been operated for chronic simple, and two for chronic congestive, glaucoma. Iridencleisis had been done upon 15 eyes, and corneoscleral trephination upon 7 eyes.

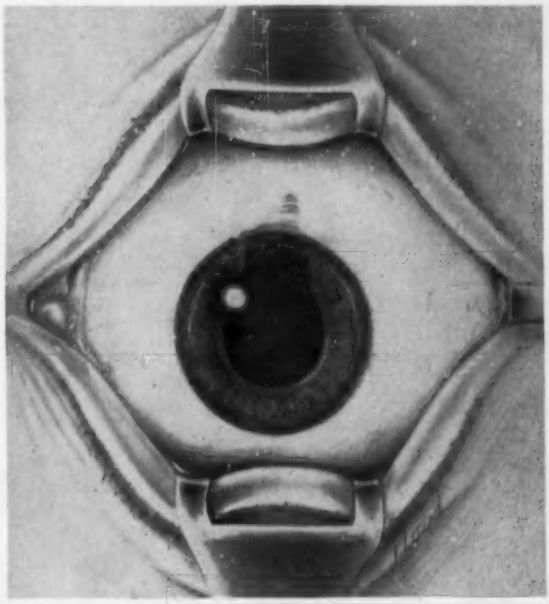


Fig. 12.—Sutures tied after extraction of lens.

Vitreous loss occurred in two eyes. In one an updrawn pupil followed, which required subsequent iridotomy. In another, as a result of postoperative iridocyclitis, a membrane formed which was incorporated with the iris. An iridocapsulotomy had to be performed, and a fair visual result was obtained. In the rest of the eyes, operation was without mishap, and the postoperative course was uncomplicated except for a choroidal detachment with a shallow anterior chamber in one. Two patients developed a shallow anterior chamber after removal of sutures, but this did not interfere with the outcome. The visual result in all instances was as good as could be expected, with the exception of the eye in which vitreous loss was encountered. Poor visual acuity in other instances had resulted from macular changes or glaucomatous optic atrophy, rather than from complications of cataract surgery. There was no instance of delayed re-formation of the anterior chamber. No eye developed subsequent rise in ocular tension or needed miotics. Follow-up

was from three months to four years. None of the eyes had hypotension before cataract extraction. The appearance of the eyes was excellent, and the absence of corneal edema was gratifying (Fig. 12).

COMMENT

This paper has reviewed some of the hazards and has discussed the advantages and disadvantages of conventional procedures for removal of cataract following filtering operations for glaucoma. A method of making a corneal section anterior to the filtering area is described. The incision is made in clear cornea, 1 mm. within the limbus, perpendicular to the corneal surface. The smallest possible overhanging

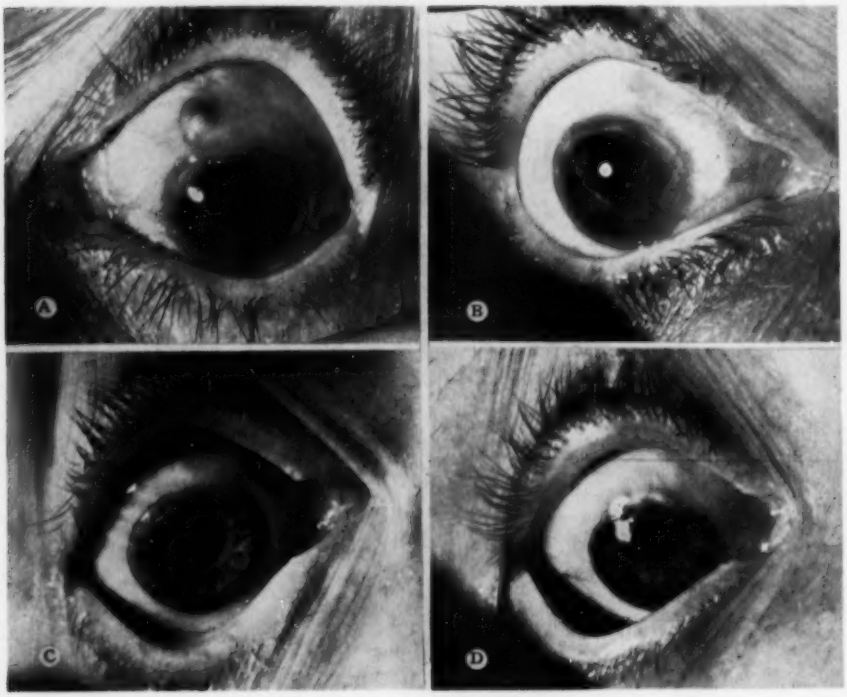


Fig. 13.—*A, B, C, D,* photographs showing preservation of filtering areas and clear cornea, except for the incisions, in three eyes having had cataract extractions following iridencleisis, and in the other following corneoscleral trephination.

ledge of cornea thus results, and good approximation from a combination of pre- and postplaced appositional sutures is obtained. This vertical type of incision results in prompt re-formation of the anterior chamber. The danger of hyphema is minimal, because the incision is placed in avascular corneal tissue. I have used a modification of this method for all cataract extractions during the past two years and believe that it offers certain advantages over the beveled type of incision.

The need for freeing adhesions of the iris to the lens before delivery of the cataract, particularly after iridencleisis procedures, is emphasized. If the pupil tends to be updrawn, a sphincterotomy should be done at 6 o'clock (Fig. 13). In this series of eyes, good visual results were obtained in all instances, and the postoperative tension was normal without miotics in all eyes.

In conclusion, the corneal incision described in this paper has given satisfactory results thus far. It has certain advantages, which have been described, for cataract extraction in eyes that have had previous filtering operations for glaucoma. The type of operative procedure to be selected, however, is still the one of preference of the surgeon. Only further comparison of results in such eyes can lead to a more rational choice of procedure.

SUMMARY

The prognosis in cataract extraction following filtering operations for glaucoma must always be guarded because of possible visual damage caused by glaucoma; alterations in the ocular tissues due to the glaucoma, as well as changes accompanying iridencleisis, trephination, or other procedure which make cataract extraction more difficult and healing more unpredictable, and, finally, the danger of rise in ocular tension following extraction.

A method of making a perpendicular corneal incision superiorly, which completely avoids the filtering area, is discussed. Results in 22 eyes operated on by this method are presented.

The management of certain difficulties in cataract extraction following filtering operations for glaucoma, other than making the incision, is outlined.

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An Optical Explanation of Hering-Hillebrand's Horopter Deviation

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The horopter is defined as the locus of the points in space whose retinal images fall on corresponding points of the two retinae. In a general way the horopter is three-dimensional, a surface that passes through the fixation point and through any other point whose images fall on corresponding retinal points.

The simplest approach to the study of the horopter is the longitudinal horopter, the line of intersection between the horopter surface and a plane through the point of fixation and the foveae of the two eyes. In the following, discussion will be limited to the longitudinal horopter and to the special case of symmetrical convergence.

Early writers on the subject attempted to ascertain the shape of the horopter from geometrical considerations. Those attempts were given a final form by Helmholtz [1] (1910). He based his calculations on the following assumptions, derived mostly from experimental data found by Volkmann.

1. The foveae are corresponding points.

2. The apparently horizontal meridians of the two retinae correspond.

3. Points on the horizontal retinal meridians, equally distant from the foveae, are pairs of corresponding points.

The conclusion reached was that the longitudinal horopter with symmetrical convergence is a circle which passes through the point of fixation and the nodal points of the two eyes (Vieth-Müller circle).

A great number of investigators have tried to determine the shape of the longitudinal horopter by means of experimental methods. The curve found in this way is called the empirical horopter. Hering found that the empirical horopter does not coincide with the Vieth-Müller circle, and subsequent workers confirmed this observation.

The empirical horopter shows considerable individual differences. The general rule, however, is as follows: At a certain distance (the abathic distance, Liebermann) it is a straight line on an objective frontoparallel plane. At a shorter distance it is concave to the face of the observer, but the curvature always seems to be less than that of the Vieth-Müller circle. At a greater distance it is convex to the face. The abathic distance is individually variable; the average is about 100 cm. (Kröncke,[2] 1921). The difference between the empirical horopter and the Vieth-Müller circle is called the Hering-Hillebrand deviation.

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The current explanation of the Hering-Hillebrand horopter deviation was given by Hillebrand [3] (1893).

One of Helmholtz' assumptions (quoted above as No. 3) was that points on the horizontal retinal meridians equally distant from the foveae are corresponding pairs. If f_1 and f_2 are the foveae and p_1 and p_2 a pair of corresponding points, p_1 on the temporal half of the retina of the left eye and p_2 on the nasal half of the retina of the right eye, the distance $f_1—p_1$ is equal to $f_2—p_2$.

According to Hillebrand, this assumption is incorrect. If $f_2—p_2$ is greater than $f_1—p_1$, the horopter deviation is explained and the exact shape of the horopter is determined by the relation between $f_1—p_1$ and $f_2—p_2$.

Hillebrand's theory explains not only the horopter deviation but also a monocular asymmetry, the well-known bisectioning experiment of Kundt (1863). The connection between the Kundt asymmetry and the Hering-Hillebrand horopter deviation has been illustrated by the experiments of Frank [4] (1905), Fischer [5] (1924), and Ogle [6] (1950).

Another possible way of explaining Hering-Hillebrand's horopter deviation is through dioptric asymmetries of the eyes. This possibility was mentioned by Hillebrand [3] and discussed by Tschermak-Seysenegg [7] (1952).

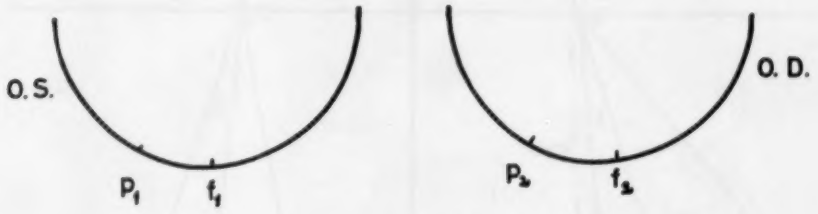

Figure 1

The present analysis is based on Helmholtz' three assumptions. Its aim is to find a possible dioptric asymmetry which explains the Hering-Hillebrand horopter deviation and to find the relations between that asymmetry and the shape of the horopter.

The usual points of departure in the calculations of the geometrical horopter are the nodal points. In actual fact, there are two nodal points in each eye. The distance between the nodal points is very small in comparison with the distance from the point of fixation to the anterior nodal point, but might not be unimportant in comparison with the distance from the posterior nodal point to the fovea. Consequently, the posterior nodal points are chosen as the centers of perspective.

In earlier calculations of the geometrical horopter, the center of curvature of the retina has been tacitly assumed to coincide with the nodal point. This is not exactly correct. The posterior nodal distance is certainly greater than the radius of curvature of the retina.

The line from the point of fixation through the posterior nodal point to the fovea is the visual axis * of the eye. If the eye is perfectly symmetrical, the visual axis of the eye must pass through the center of curvature of the retina. However, this is improbable. If the geometrical axis of the retina is defined as a line through

* The *Gesichtslinie* of Helmholtz.

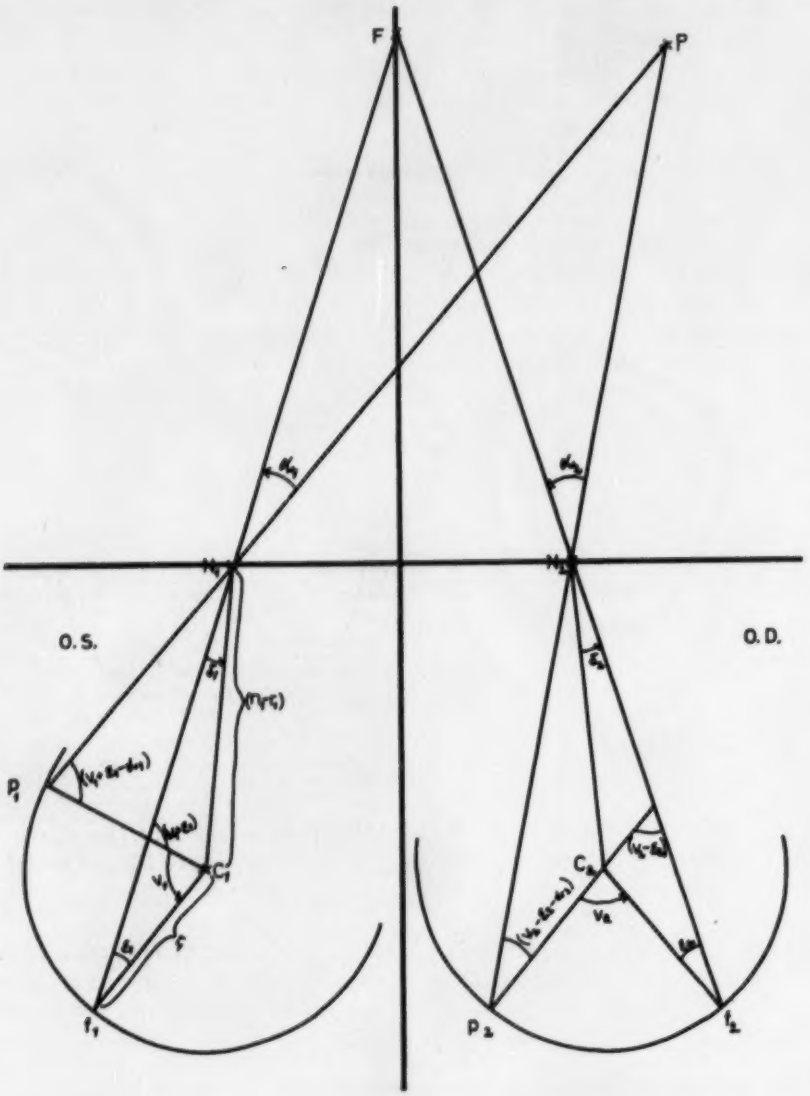

Figure 2

the posterior nodal point and the center of curvature of the retina, this axis will intersect the retina at some point at a finite distance from the fovea. The angle between the visual axis of the eye and the geometrical axis of the retina, the angle δ, is a measure of an important part of the asymmetry of the eye. The magnitude of this angle is unknown, and it seems impossible to measure it directly.

In Figure 2, F is the point of fixation; P, a point on the horopter. N_1 is the posterior nodal point, C_1 the center of curvature of the retina, f_1 the fovea, p_1 the retinal image of point P, n_1 the posterior nodal distance measured along the geometrical axis of the retina, r_1 the radius of curvature of the retina, v_1 the angle

$f_1C_1p_1$, and a_1 the angle FN_1P; δ_1 is the angle between the geometrical axis of the retina and the visual axis of the eye; ϵ_1 the angle $C_1f_1N_1$, all in the left eye. N_2, C_2, f_2, p_2, n_2, r_2, v_2, a_2,δ_2, and ϵ_2 are the equivalent points, distances, and angles in the right eye.

On the assumption that the distance f_1—p_1 is equal to f_2—p_2, it is immediately evident that the angles v_1 and v_2 must be equal.

The sine theorem is used in the calculation of the angles ϵ_1 and ϵ_2.

$$\frac{n_1-r_1}{r_1}=\frac{\sin\epsilon_1}{\sin\delta_1}$$
$$\frac{n_2-r_2}{r_2}=\frac{\sin\epsilon_2}{\sin\delta_2}$$

According to the theorem on supplementary angles of triangles, the angle $C_1p_1N_1=(v+\epsilon_1-a_1)$ and the angle $C_2p_2N_2=(v-\epsilon_2-a_2)$. By using the sine theorem, the following is obtained:

$$\frac{n_1-r_1}{\sin(v+\epsilon_1-a_1)}=\frac{r_1}{\sin(a_1+\delta_1)}$$
$$\frac{n_2-r_2}{\sin(v-\epsilon_2-a_2)}=\frac{r_2}{\sin(a_2-\delta_2)}$$

Hence the following equation systems are obtained:

$$\left.\begin{aligned}\sin\epsilon_1&=\frac{n_1-r_1}{r_1}\sin\delta_1\\ \cot a_1&=\frac{\cos(v+\epsilon_1)+\frac{n_1-r_1}{r_1}\cos\delta_1}{\sin(v+\epsilon_1)-\sin\epsilon_1}\end{aligned}\right\}\quad(1)$$

$$\left.\begin{aligned}\sin\epsilon_2&=\frac{n_2-r_2}{r_2}\sin\delta_2\\ \cot a_2&=\frac{\cos(v-\epsilon_2)+\frac{n_2-r_2}{r_2}\cos\delta_2}{\sin(v-\epsilon_2)+\sin\epsilon_2}\end{aligned}\right\}\quad(2)$$

It is very laborious to calculate the shape of the horopter from Equations (1) and (2), even if the values of the constants in the equations are known. The work is simplified by the use of Ogle's [6] (1950) formula for the analysis of horopter data.

$$\cot a_1-R_o\ cot\ a_2=H$$

In this, a_1 and a_2 are defined as above but, as Ogle measures those angles in the negative direction, with the opposite signs. The constant H describes the curvature, and R_o, the skewness of the horopter curve. Ogle has shown that the constant H can be used as a measure of the Hering-Hillebrand horopter deviation. "For the condition H=0 the curve coincides with Vieth-Müller's circle. As H increases positively the curve departs from Vieth-Müller's circle and its curvature becomes less. When $H=\frac{2a}{b}$ (in this $2a$ is the distance between the nodal points and b the distance from the point of fixation to a straight line between the nodal points) the curve becomes a straight line at the fixation point and coincides with the objective fronto-parallel plane. If H is greater than $\frac{2a}{b}$ the curve becomes convex to the subject."

In Ogle's formula, R_o describes the degree to which the curve is skew in respect to the objective frontoparallel plane of the observer. If the convergence is symmetrical, the posterior nodal distances n_1 and n_2 are equal, and the angles δ_1 and δ_2 are symmetrical and equal, the horopter will be symmetrical and the value of the constant R_o equal to unity.

If we assume that $n_1=n_2$, $r_1=r_2$, $\delta_1=\delta_2$, and, consequently, $\epsilon_1=\epsilon_2$ and $R_o=1$, it is possible to find the value of H from Ogle's formula and Equation systems (1) and (2).

$$\left.\begin{aligned} H=&\frac{\cos(v-\epsilon)+\frac{n-r}{r}\cos\delta}{\sin(v-\epsilon)+\sin\epsilon}-\frac{\cos(v+\epsilon)+\frac{n-r}{r}\cos\delta}{\sin(v+\epsilon)-\sin\epsilon}\\ &\sin\epsilon=\frac{n-r}{r}\sin\delta \end{aligned}\right\} \qquad (3)$$

Equation (3) measures the relation between angle δ and the shape of the horopter. Angle δ is, however, only one of the possible asymmetries of the eye and gives the relation between the optical apparatus and the retina. The monochromatic aberrations of the optical apparatus, especially distortion, might also influence the shape of the horopter. This influence is naturally very difficult to calculate, but a short discussion of a very simple special case might be of interest. Let it be assumed that all optical data of the two eyes are equal and the angle δ is zero. If the eyes were ideally corrected for distortion, $a_1/v=a_2/v=$const. If distortion is present, a_1/v and a_2/v are functions of v. But for each value of v, a_1/v will be equal to a_2/v, and $a_1=a_2$. In this special case $H=0$, and the horopter coincides with Vieth-Müller's circle. Distortion alone cannot explain Hering-Hillebrand's horopter deviation, but if δ differs from zero, distortion will influence the value of H. If v and δ are small, this influence will be unimportant. Consequently, Equation (3) is valid for small values of v, δ and ϵ.

If v and ϵ are small and interchangeable with their sines, a considerable simplification of Equation (3) is possible. The approximate solution is then

$$H=2\frac{n-r}{r}\sin\delta \qquad (4)$$

From known optical data it is possible to calculate the posterior nodal distance. Stenström's [8] (1946) mean values of the refracting power of the cornea (42.84 D) and the length of the optical axis of the eye (24.00 mm.) were used. If the index of refraction of the aqueous and vitreous is 1.366 and the distance from the vertex corneae to the optical center of the lens, in agreement with Gullstrand's † (1909) simplified schematic eye, is 5.85 mm., the calculated value of the posterior nodal distance is 16.72 mm. This distance is measured along the visual axis of the eye, and n in Equation (4), along the geometrical axis of the retina. If angle δ is small, the difference will, however, be insignificant.

Lo Cascio [9] (1922) has made careful measurements of the curvature of the posterior part of the eye. It is, in fact, not spherical, but within the macula lutea a sphere with a radius of 11.33 mm. gives a reasonably good approximation.

If $n=16.72$ and $r=11.33$, $(n-r)/r=0.48$. $H=0.96\sin\delta$, or, approximately, $H=\sin\delta$.

In general, experimental data of the longitudinal horopter curves correspond to positive values of H. A negative value of H would give a horopter of greater curvature than Vieth-Müller's circle. The positive sign of Equation (4) means that angle δ is positive. The signification of this is that the geometrical axes of the retinae are divergent in comparison with the visual axes. The angle between the optical axis of the cornea and the visual axis, as a rule, has the same sign.

Empirical determinations of Hering-Hillebrand's horopter deviation are time-consuming and can be performed with precision only by trained subjects. Each investigator has had to confine himself to examining a small number of subjects.

† Gullstrand, in Helmholtz,[1] Vol. I.

The arrangement of the experiments has shown variations, and the results of different investigators are not directly comparable. The result is that mean values of H are not available.

Not all empirical values of H are useful for our present purpose. As Equation (4) is valid only for small values of v, the determinations of H should have been performed within the central part of the horopter. The distance of observation should not be too short, since the value of n is influenced by accommodation. With the limits of v at $\pm 6°$ and the distance of observation of $\geqq 40$ cm., the value of H very seldom appears to exceed 0.15, with the majority of values between 0.05 and 0.10. A value $H=0.10$ corresponds to an angle δ of about 6 degrees. Values of δ of that order of magnitude do not seem unlikely.

Ogle has shown that H is a constant, independent of the value of α_2 and, consequently, also of v. This empirical finding agrees perfectly with Equation (4).

The possibility of finding a mathematical relation between angle δ and H does not demonstrate that Hering-Hillebrand's horopter deviation is purely a function of angle δ. Such proof is possible only by direct measurement of angle δ combined with determination of H in a sufficient number of subjects, but direct measurement of angle δ does not seem practicable. It is possible that Hillebrand's hypothesis is correct, i. e., that the distribution of corresponding retinal points is asymmetrical. The relation between the distribution of corresponding retinal points and the shape of the longitudinal horopter must, however, be determined by the angle δ.

SUMMARY

Hering-Hillebrand's horopter deviation is not necessarily the result of an asymmetrical distribution of corresponding retinal points. It might be caused by dioptric asymmetries of the eye. An important part of the asymmetry of the eye is measured by the angle δ between the optical axis of the eye and the geometrical axis of the retina. If n is the posterior nodal distance of the eye, r the radius of curvature of the retina, and H Ogle's measure of Hering-Hillebrand's horopter deviation, the relation between δ and H is given by the equation

$$H=2\frac{n-r}{r}\sin\delta$$

The validity of this equation is limited to the central part of the longitudinal horopter.

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Resection Under Tenon's Capsule

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In 1954 Talbot and I reported a technique of recessing a rectus muscle under Tenon's capsule.[1] In this technique the conjunctival incision is made parallel to the muscle insertion but is placed near or behind the equator. By this means postoperative irritation of the sutures and visible scarring are minimized. Tenon's capsule then is incised parallel to and over the muscle to expose the muscle insertion. After recession of the muscle insertion, Tenon's capsule and the conjunctiva are closed with fine absorbable sutures so that the normal relationship of Tenon's capsule to the conjunctiva is retained. In the usual procedures both Tenon's capsule and the conjunctiva are incised parallel to the muscle insertion near the limbus. The flap of Tenon's capsule over the muscle generally is allowed to retract with the recessed muscle. This contracted flap of Tenon's capsule often forms a cicatricial mass under the conjunctiva, reducing effectiveness of the procedure and disturbing the structures of the inner canthus. Also, the conjunctiva may become adherent to the exposed sclera, particularly to the original insertion of the muscle.

Since publication of the article on recession under Tenon's capsule, I have received numerous requests as to how this technique could be applied to the resection operation. It is the purpose of this report to illustrate the technique of resection of the medial rectus muscle as it is now performed at the University of Oregon Medical School Hospitals.

For a resection operation the medial rectus muscle is exposed in the same manner as for a recession operation (Fig. 1*A* and *B*). Thereafter, the technique of resection differs in several significant aspects. For example, Gifford and Berens,*

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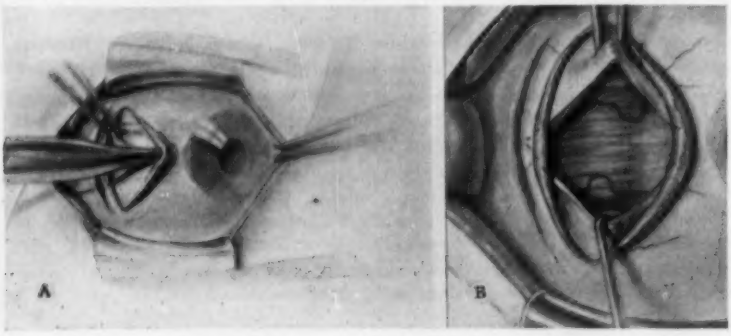
From the Department of Ophthalmology at the University of Oregon Medical School.

* References 2 and 3.

Fig. 1.—*A*, the conjunctiva is incised just anterior to the plica and is stripped back to expose Tenon's capsule. To avoid tearing the fragile conjunctiva, only Tenon's capsule is grasped with forceps. *B*, Tenon's capsule is incised parallel to the muscle and is retracted.



in reoperations, have found that the effectiveness of resection operations frequently is lost by adherence of the muscle belly to the sclera behind the desired insertion. This complication most commonly occurs because the thin capsule which covers the muscle is traumatized or is destroyed. This capsule is formed by splitting of the "intermuscular membrane" over the muscles. This is a thin membrane extending around the globe in the equatorial region between the four rectus muscles. If this membrane is incised close to the muscle, it will retract, baring the fibers. For this reason, this membrane should be buttonholed and incised at least 2 mm. from each side of the muscle (Fig. 2*A*). Also, the buttonhole should extend completely through the membrane down to the sclera before a hook is passed under the muscle. Forceful passing of the muscle hook through the membrane and under the muscle may strip away the membranous covering of the underside. The reflections of the muscle capsule to Tenon's capsule are severed by sharp dissection (Fig. 2*B*). It will be noted in Figure 3 that the muscle is cut without the use of a clamp. It is

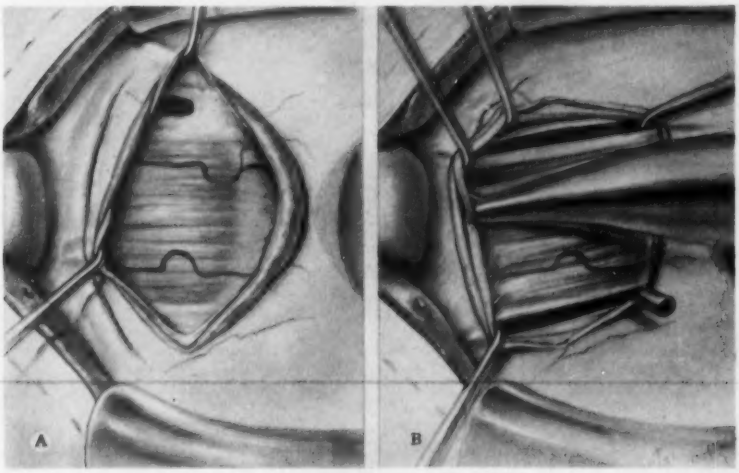


Fig. 2.—*A*, the intermuscular membrane is buttonholed at least 2 mm. from the muscle. Incisions made closer to the muscle may allow the capsule to retract and bare the muscle fibers. *B*, the buttonholes are extended to parallel incisions, and a hook is passed under the muscle. Reflections from the muscle to Tenon's capsule are severed.

my feeling that a muscle clamp, if used, should be placed on that part of the muscle or tendon which will be excised; otherwise, traumatized tissue is retained. Placement of the sutures before the muscle is cut obviates the need for a clamp. Also, it permits more accurate placement of the sutures across the muscle.

It generally is recognized that there is much greater stress on the sutures in resection than in recession operations. Also, the slipping of sutures has greater significance. Whereas a slight slipping of the muscle attachment generally has little or no effect on the outcome of a recession operation other than to increase the amount of recession, a slip of the muscle ending of only 1 to 2 mm. in a resection operation may appreciably reduce the effectiveness of the procedure. This is so because the muscle end in slipping back generally attaches to the sclera behind the original insertion. A firm and exacting apposition of the entire cut edge of the muscle with the old insertion, therefore, is crucial to the success of the resection procedures. Three evenly spaced O'Brien locked stitches achieve this objective

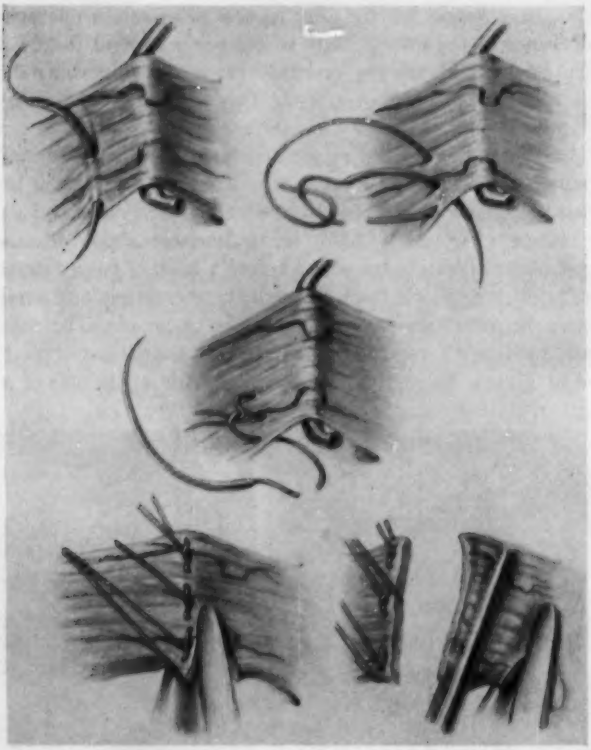
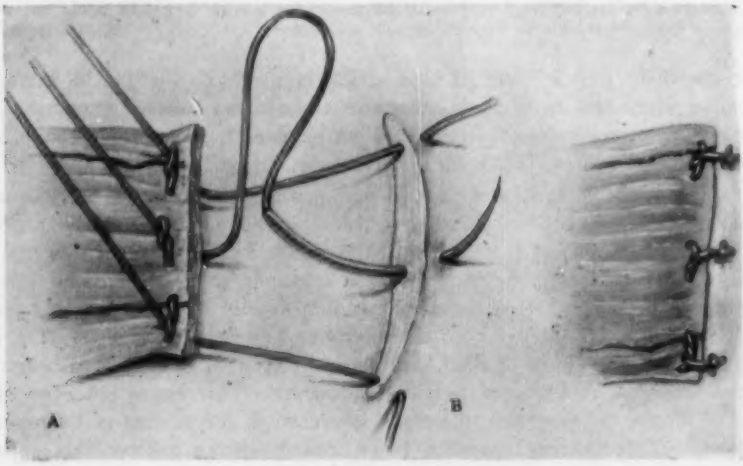


Fig. 3.—O'Brien lock stitches are placed before the muscle is resected. Elevation of the muscle on a hook facilitates placement of the sutures.

Fig. 4.—*A*, the sutures are passed through the edge of the scleral stump to approximate accurately the cut end of the muscle with the old insertion. *B*, the knots are tied on the scleral side of the incision to minimize pressure on the muscle fibers.



(Fig. 3). They are less apt to tear out than simple radial sutures and do not bunch the muscle like mattress sutures. The sutures are passed through the stump of the insertion so as to produce an accurate end-to-end apposition (Fig. 4*A*). Knots tied in direct contact with the muscle fibers tend to produce necrosis of these relatively friable tissues; therefore, it is best to place the knots on the scleral side of the insertion (Fig. 4*B*).

In most techniques of resection, nonabsorbable sutures are used, with knots tied on the outer surface of the conjunctiva. These sutures, which extend from the muscles out through the conjunctiva, act as open pathways from the exterior to the muscle ending. It is my belief that postoperative reaction with its undesirable secondary cicatricial reaction is less if buried absorbable sutures are used and the operative site is completely covered. At present, 00000 mildly chromatized absorbable surgical suture U. S. P. is being used at the University of Oregon Medical School. Then Tenon's capsule and the conjunctiva are closed separately with 000000

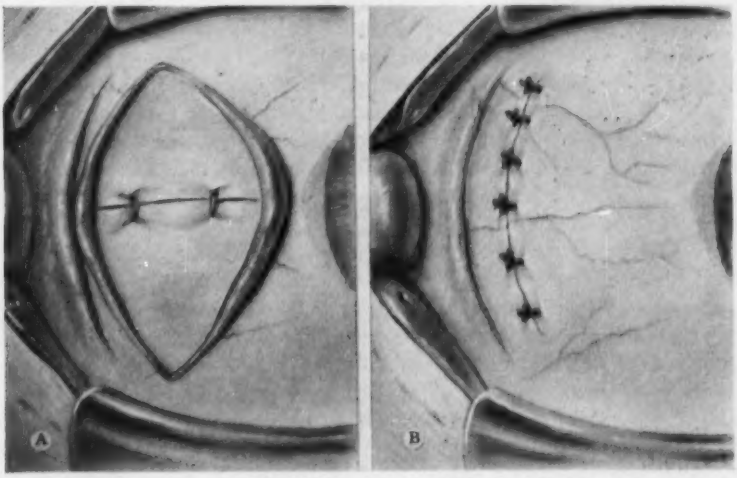


Fig. 5.—*A*, Tenon's capsule is accurately closed with fine absorbable sutures. The knot is placed under the capsule. *B*, conjunctiva is closed with fine absorbable sutures.

mild chromic absorbable surgical sutures. The sutures through Tenon's capsule are inverted and buried (Fig. 5*A*). Interrupted sutures are used in the conjunctiva (Fig. 5*B*).

There are several points in the technique which we have found helpful in reducing postoperative reactions. The lid margins are almost completely covered by the use of a wide, solid-bladed, notched speculum of the type designed by Keizer.[4] The lids are covered by a self-adjusting drape, so that sutures have no opportunity to become contaminated by contact with the skin. In the operation, sponges are not used. Talbot and Christensen have found that shredding from sponges is an important factor in establishing cicatricial reaction under the conjunctiva and in the extraocular muscles.[5] They found cotton strands to adhere readily to Tenon's capsule. There is little bleeding in the course of a resection operation; therefore, adequate hemostasis can be obtained with vasoconstrictors and suction. For a suction tip, a piece of flexible polyethylene tubing is highly satisfactory. The edge is beveled, and a hole is made in the side of the tube to minimize the sucking of tissues up into the tube.

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Corneoscleral Trephine Operation

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In chronic simple, or "wide-angle," glaucoma the treatment of choice is medical. In the early stages weak miotics should be used and their strength and frequency increased sufficiently to control the intraocular pressure and preserve the visual field. In cases where this is not accomplished satisfactorily some type of filtering operation should be done. The patient should be apprized of this fact and told that the time has come when surgery should be performed. He is told that surgery offers the best chance for the preservation of vision and the visual field for the longest period. Because of the nature of the disease, the uncertainties regarding the final result in all cases of glaucoma should always be explained.

It is our feeling that the procedure of choice in this type of glaucoma is the corneoscleral trephine operation, provided it is done with the proper considerations: First of all, the selection of the proper-sized trephine blade is most important. This was pointed out by Chandler a number of years ago. In younger patients, under 45 or 50, a blade of larger diameter, at least 2 mm., should be used. In patients 55 or older, a blade of smaller diameter, 1.5 to 1 mm., should be used. The reason for this selection is the varying state of the conjunctiva at the different ages. In the younger person the conjunctiva is definitely thicker and more vascular, whereas in the older person it is much thinner and more atrophic. If the larger blade is not used in younger patients, the opening is very likely to be closed by the thick conjunctiva. In the older patient, if the larger blade is used, the patient may have a soft, watery eye and complain of a large lump under the lid. It goes without saying that any trephine blade used should be perfect and sharp. This condition, however, is sometimes very difficult to obtain. Other considerations will be discussed under "Technique."

ANESTHESIA

1. The corneoscleral trephine operation is easily performed with topical anesthesia alone. This method should be employed whenever possible, with adequate preoperative sedation.

2. If the patient is at all nervous or apprehensive an O'Brien lid block may be given, as well as a retrobulbar injection of 2% procaine with hyaluronidase (Wydase). At the discretion of the surgeon, a small amount of 2% procaine may be injected under the upper bulbar conjunctiva near the limbus (Fig. 1). In some very nervous patients thiopental (Pentothal) sodium may be given intravenously.

TECHNIQUE

The type, shape, and size of the conjunctival flap are very important. I prefer to grasp the conjunctiva with small toothed forceps (Bishop-Harman) about 7 mm.

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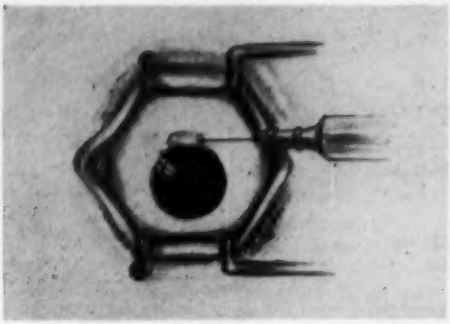

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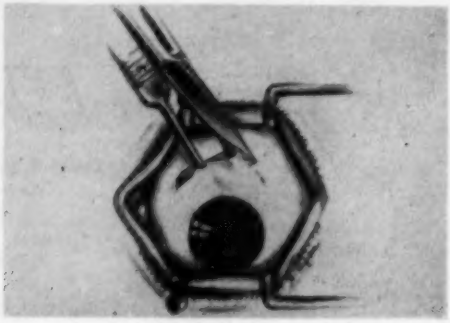

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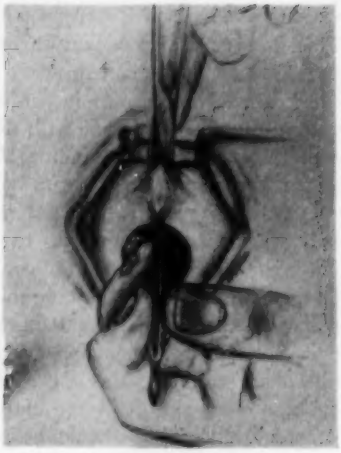

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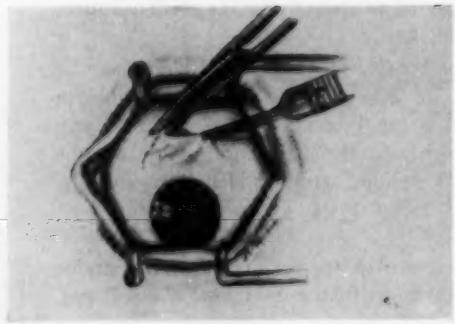

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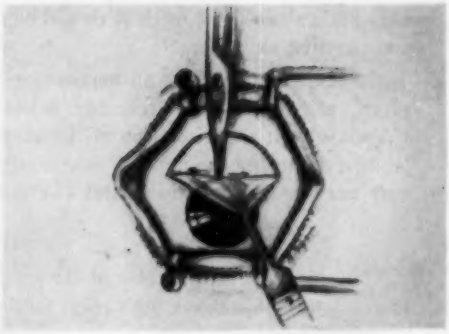

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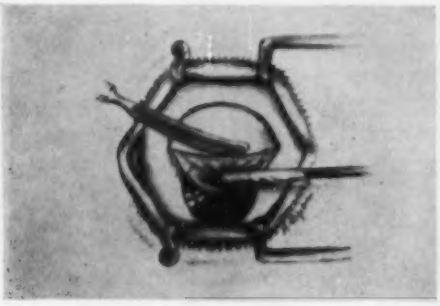

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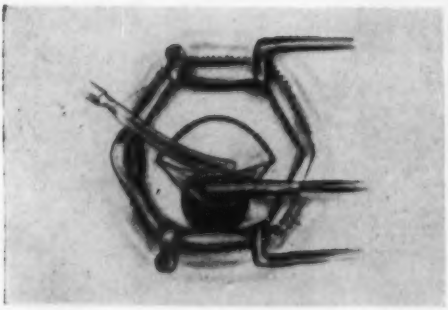

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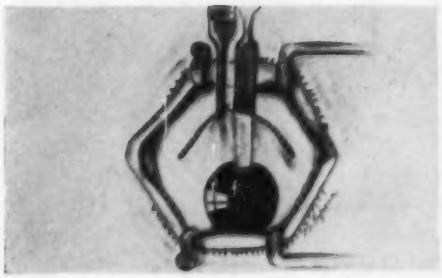

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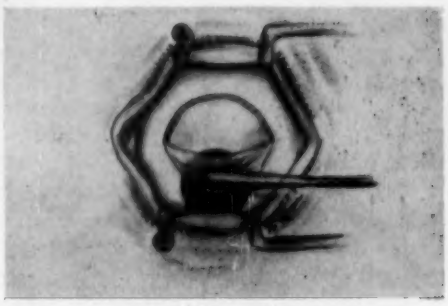

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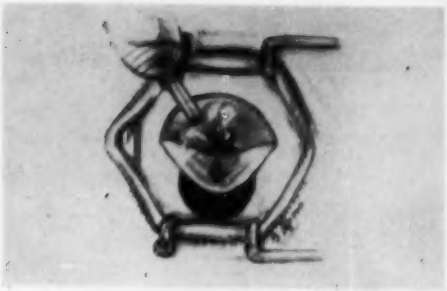

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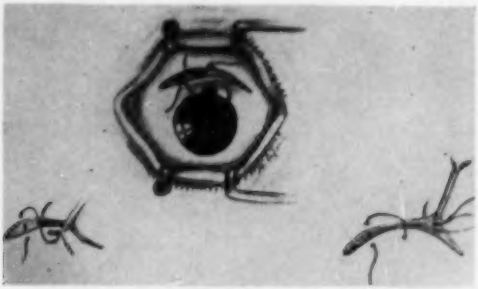

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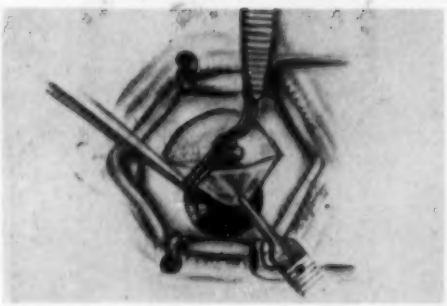

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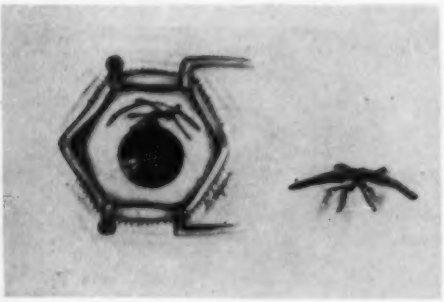

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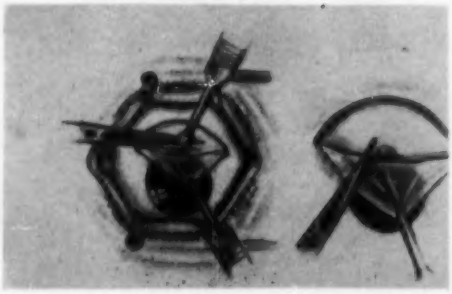

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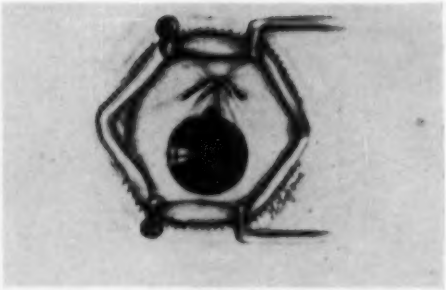

Figure 17

back of the limbus above in the 12 o'clock meridian, drawing this upward and forward. At the same time an incision is made through the conjunctiva with the Stevens scissors just behind the forceps, and anterior to the insertion of the superior rectus muscle (Fig. 2). This incision should be made through Tenon's capsule and all the way down to the sclera itself. A second grasp is then taken with the same forceps, making sure that Tenon's capsule is engaged in the teeth. Two other incisions are then made from this point with the Stevens scissors, one down and nasally (Fig. 3), the other down and temporally (Fig. 4), for a distance of about 0.5 cm. on each side; but these incisions do not go all the way to the limbus. They should stop at least 4 to 5 mm. short of the limbus in order to leave a pocket to hold the aqueous for a while at least, and thereby encourage the formation of a bleb. Blunt dissection is then carried all the way down to the limbus with the tips of the Stevens scissors, making sure that all the episcleral tissue, including Tenon's capsule, is dissected free from the sclera (Fig. 5). Any points of bleeding should be controlled with a ball-tip cautery. After the limbus has been reached, the forceps is removed from the conjunctival flap, and a moistened cotton applicator is placed on the undersurface of the flap, after it has been everted and pulled down. Pressure is made with this downward, pushing and drawing the conjunctival flap taut over the anterior surface of the cornea. This maneuver serves as fixation of the globe, and at the same time it stretches the conjunctiva and prevents buttonholing while splitting the cornea. The Fox corneal knife is then used to split the cornea or, even better, peel away the corneal epithelium and Bowman's membrane for a distance of about 1 to 1.5 mm. (Figs. 6 and 7). This maneuver requires good illumination and magnification. The strokes of the Fox knife should be deliberate and firm, the surgeon using mainly the rounded tip directed in a plane parallel to and just beneath Bowman's membrane. If the procedure is carried out in this way, a good plane of cleavage is found and maintained, enabling one to split the cornea quite easily. Many operators go too deep into the corneal stroma, trying to avoid perforation of the flap. This results in a rigid ledge of corneal stroma, which makes proper placement of the trephine blade very difficult. Naturally, the assistant should keep the field absolutely dry by pressing a tightly wound cotton applicator firmly against the wound as it is being made in the cornea. Wiping or dragging strokes should never be made, since these are very likely to tear or perforate the conjunctival flap. The depth of the incision or dissection into the cornea should be checked with an iris repositor, by placing this into the wound and flipping the conjunctival flap back over its tip and observing just how far the tip extends into the cornea (Fig. 8). This is sufficient when one can place the trephine blade on the limbus so that one-half will lie on the cornea and one-half on the sclera (Fig. 9). The trephine blade should be placed in position very carefully while the conjunctival flap is held down with the cotton applicator, keeping it taut, as described, so as to avoid nicking the conjunctiva, with the anterior edge of the blade. The blade is slid down and forward more or less from the scleral side onto the corneal side in order to be certain that no conjunctiva or corneal epithelium is engaged under the blade (Fig. 10). The top of the chuck of the trephine is then tilted downward toward the patient's feet, and the operator holds this lightly between his thumb and middle finger, leaving the index finger free to control the amount of tilt and pressure (Fig. 11). No pressure is necessary, however, and this should be avoided whenever possible. The blade should be sharp enough to cut with its own weight. The chuck is then rotated between the thumb and the middle finger, making half-turns back

and forth until the patient complains of a slight amount of pain. The trephine blade should then be lifted and removed. If successful, a circular button of one-half cornea and one-half sclera should then be everted outward and upward by a prolapse of iris and a sudden evacuation of aqueous (Fig. 12). This button should be hinged on the scleral side if the blade has been properly placed and tilted. The iris should be grasped immediately with iris forceps and pulled out between the blades of the De Wecker scissors, which are held parallel to the limbus and pressed downward against the cornea and sclera as the iris is cut. The sphincter should be included and a complete iridectomy done. The assistant should be holding the conjunctival flap with fine forceps down and away from the prolapsed iris and the De Wecker scissors while the iridectomy is being performed (Fig. 13). After the iridectomy, the assistant should hold the conjunctival flap in the same way while the button of cornea and sclera is grasped with the iris forceps and the scleral hinge cut free with sharp-tipped iris scissors, making certain to include all the scleral fibers, which sometimes are not entirely cut through, but at the same time being careful not to injure the ciliary body or vitreous (Fig. 14). No attempt should ever be made to enter the anterior chamber to pick up the iris with forceps. This should never be necessary if the proper pressure is made over the conjunctival flap and cornea with the cotton applicator, as described. The final step is to suture the conjunctiva with a #5 twisted black silk suture, taking only two bites, the first through the anterior and posterior lips of the conjunctival wound about 3 to 4 mm. from the temporal or nasal side (Fig. 15), the second in a similar fashion about 4 mm. from the first and about 4 mm. from the other end of the incision. This is done in a whipstitch fashion, and the ends of the suture are brought together and tied in a single knot (Fig. 16). This causes the conjunctival flap to pucker like a tent; this helps to encourage a conjunctival bleb (Fig. 17).

POSTOPERATIVE CARE

1. Atropine 1% is instilled and the eye patched. The eye not operated on is left open for miotic drops, which should be instilled then and every three hours for at least 24 hours after the operation and less frequently thereafter.

2. Atropine should be instilled in the eye operated on daily at the time of dressing and continued until the eye is white. Light digital palpation, or massage, should be started early to encourage and maintain a satisfactory conjunctival bleb with filtration. The conjunctival suture is removed on the fourth or fifth day, at which time the patient is allowed out of bed. If there have been no serious complications, the patient is discharged from the hospital on the seventh or eighth day. The patient should be seen at the surgeon's office two or three days later, and at least once a week thereafter, until the eye is entirely quiet and the tension has become normal.

SUMMARY

The failure of medical treatment to control the intraocular tension and prevent the loss of the visual field is given as the indication for surgery in "wide-angle" glaucoma.

The procedure of choice is the corneoscleral trephine operation. Attention is stressed with regard to the following points: 1. The type of conjunctival flap is important, it being made certain that the incision of the flap does not go all the way down to the limbus and that all bleeding points are stopped with cautery.

2. The size of the trephine blade should be chosen with consideration to the age of the patient. 3. The trephine blade should be placed so that the top of the blade, or chuck, is tilted toward the patient's feet. This is done to cut through the corneal side of the button first. 4. Pressure and traction on the conjunctival flap should be made with a moist cotton applicator to keep the conjunctiva taut and encourage the prolapse of iris when the corneal scleral button is cut through. 5. The iris should be grasped first and a complete basal iridectomy done. 6. The corneal scleral button is then excised with sharp-pointed scissors, and all remaining fibers of sclera, which may have shaled off, should be removed. Extreme care should be taken not to injure the ciliary body or vitreous. 7. The conjunctival wound should be closed with a special short running suture to encourage puckering and filtration. This suture is tied in only one knot to make its removal easier. 8. Atropine should be used daily in the eye operated on until it is entirely white. 9. Digital massage should be started early and continued until the conjunctival bleb is satisfactory. 10. Miotic drops should be continued in the intact eye if these are controlling the tension and visual field; otherwise, a corneoscleral trephine operation should be done on this eye one week after it has been done on the first eye.

Our experience with the corneal trephine operation, as described, has been very satisfactory. Many of the objections made by some to the standard trephine operation are reduced or almost eliminated. Some of these objections are (1) quiet iritis; (2) excessive hemorrhage; (3) closure of the trephine opening, with a nonfiltering conjunctival bleb and subsequent rise of intraocular pressure; (4) too large a bleb with a soft eye, and sometimes detachment of choroid and/or retina; (5) proliferation of uveal pigment with secondary cataract; (6) other late complications, such as infection, etc.

In recent years a great many ophthalmic surgeons are doing and advocating some type of iris inclusion operation for "wide-angle" glaucoma. The rationale for this procedure is difficult to understand, since in doing an inclusion operation one is deliberately creating a situation, an iris incarceration, which for years we have all been taught to try to avoid, and to relieve when it occurs. This is particularly true in cataract surgery and in traumatic perforations. Perhaps our ideas concerning exciting causes of sympathetic inflammation have been wrong, since so few cases of sympathetic ophthalmia following iris inclusion operations have been reported. However, one needs to have only one such case to make a tremendous difference in his thinking regarding this procedure. We should like to commend the corneoscleral trephine operation as described, and we feel that it will prove satisfactory in the majority of properly chosen cases of "wide-angle" glaucoma.

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Eye Movement Responses to Convergence Stimuli

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In previous studies * investigations were reported concerning the time characteristics of two of the most commonly executed types of eye movements, the so-called saccadic movements and the "smooth" movements elicited by moving visual stimuli. These are all conjugate movements, i. e., movements in which the two eyes move in parallel.

Disjunctive eye movements, i. e., movements in which changes take place in the orientation of one eye with respect to the other, are known to have time characteristics quite different from those of conjugate movements. Of particular interest in this connection are the movements of convergence and divergence during which the primary lines of sight of the two eyes remain in the same plane but change their relative orientation. They were first studied rather thoroughly by C. H. Judd.[3] His method, however, did not enable him to obtain continuous records of eye positions. More recently they formed the subject of a detailed analysis by Stewart.†

The usual stimulus for a convergence movement is the presentation of an object closer than infinity. The convergence response obtained under these conditions is usually associated with an accommodation response and a pupil contraction: the so-called near "reflex." Vergence movements unassociated with accommodation [4] or pupil responses [5] may, however, be obtained by presenting a pair of images seen with small degrees of binocular disparity. Such movements are called fusional movements.

The experiments to be described were carried out to ascertain the time characteristics of eye movements elicited by the presentation of visual stimuli in horizontal disparity.

Usually the eyes remained at a fixed level of convergence and stimuli were presented in crossed or uncrossed disparity requiring a convergence or divergence movement to reestablish fusion. Since all stimuli called for either a positive level of convergence or no convergence, reference will be made to movements of convergence and of convergence relaxation.‡ Preliminary studies indicate that actual

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* References 1 and 2.

† Stewart, C. R.: A Photographic Investigation of the Lateral Fusional Movements of the Eyes, unpublished Ph.D. dissertation, The Ohio State University, 1951.

‡ The term convergence relaxation is used here to denote an eye movement during which the two lines of sight change from a converged position to one of less convergence. It is used to reserve the term divergence to the movement bringing the lines of sight into a diverged position.

divergence responses, i. e., rotations of the lines of sight beyond parallelism, are not easily elicited. Divergence movements of small extent were found to have very much the same characteristics as convergence relaxations of the same magnitude near the parallel position of the eyes.

METHOD

Recording of Eye Movements.—The apparatus has been described in detail previously.[1] The subject's head remained firmly positioned by means of a bite board with a wax impression of his teeth. Reflections of a light source in each of the subject's corneas were imaged on continuously moving photographic film. Only the horizontal movements were recorded. The precision of the record is 5-10 minutes of arc in the movement direction and about 1 msec. in the time dimension. An auxiliary light source was also imaged on the film, providing a stimulus and base line. It was interrupted 100 times a second by a chopper disc, and a time scale was thus established on the film.

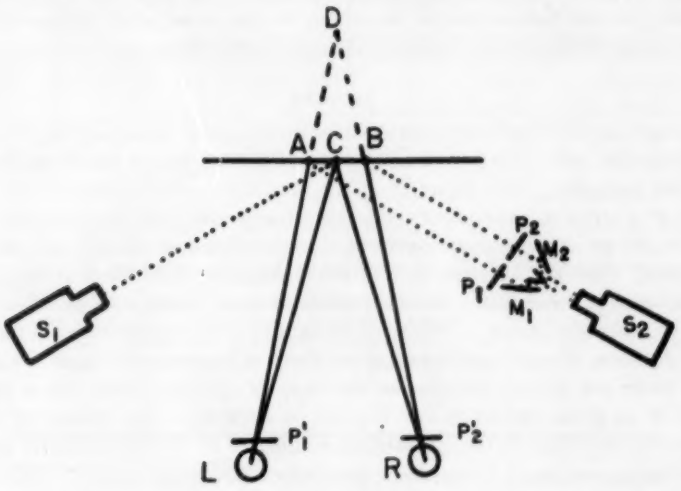

Fig. 1.—Apparatus for presenting disparate stimuli. See text for description.

Stimulus Presentation.—Facing the observer at a distance of 135 cm. was a vertically positioned aluminized screen. A single spot of light, 11 mm. in diameter, could be projected on the screen by means of projector S_1 (Fig. 1). Another projector, S_2, also produced a spot image of the same size; but the beam coming from it was split, and each half was reflected by one of the two mirrors, M_1 and M_2, before reaching the screen. This produced a doubling of the image, and the separation of the resulting two spots, A and B, could be varied by a rotation of the two mirrors with respect to each other. The two beams which finally produced spots A and B were passed through polarizing elements P_1 and P_2, whose planes of polarization were perpendicular. This polarization was retained by the aluminized screen. Another pair of polarizing elements, P_1' and P_2', correspondingly oriented, was placed before the eyes. As a result, spot A could be seen only by the left eye and spot B only by the right eye; this resulted in a visual configuration corresponding to the presentation of a spot in a position D, beyond the plane of the screen. A fixed amount of convergence was required to see point C, in the plane of the screen. For the average observer at this observation distance it was about 1.5 degrees. By means of a lever controlling the separation of the mirrors M_1 and M_2, spots A and B could be symmetrically separated so that different amounts of convergence were necessary to fuse them. Since the optical projection was confined to the plane of the screen, no changes in accommodative stimulation were associated with these changes in convergence stimulation. An electromagnetic

shutter system enabled the simultaneous blocking of the beam from one projector and exposing of the image or images from the other projector. Synchronously, a glass plate was deviated in the path of the auxiliary beam to the camera, thus indicating the change of the stimulus by a displacement of the signal line on the film.

In this manner it was possible to provide instantaneous stimuli to convergence or divergence unassociated with changes in such other stimulus dimensions as accommodation requirement, size, distance, and luminance.

Usually stimulus *C* was arranged to lie exactly midway between *A* and *B*. Changing from projector S_1 to projector S_2 then involved a stimulus to convergence relaxation or divergence if the arrangement was as illustrated in Figure 1. If *A* and *B* were crossed, it required a convergence movement on the part of the subject to reestablish fusion.

The procedure was to have the subject fixate spot *C*. This was replaced by a disparate configuration for a short period, which was then again replaced by *C*.

In one series of experiments, *C* was moved to be in exactly the same position as *A*, and *A* and *B* were crossed. This stimulus condition corresponded to that of the Panum-Wheatstone *Grenzfall*, in which one object is placed nearer than another, but on the line of sight of one eye. Seemingly, changing fixation from the distance to the near object would involve movement of only one eye, since the other is already sighting on the near object.

RESULTS

Eye movement records were obtained on three normal young adults. The results to be described are typical of all subjects, and, except where noted, no significant individual variations were found.

The first series of experiments concerned themselves with the question whether a subject always carries out a movement of convergence or convergence relaxation, as required, when the only cue to him is the disparity. The question is somewhat abstract, since under ordinary viewing conditions there is rarely a doubt which of the two movements is required; a variety of monocular or perceptual cues aid the subject in this decision. From psychophysical studies [6] it appears that most subjects are able to make the correct decision on the basis of disparity alone for a high percentage of all presentations at low degrees of disparity. The method of stimulus presentation employed in this experiment eliminates all but the disparity cue.

Eye movement records were obtained when the single spot *C* (Fig. 1) was suddenly replaced by a pair of images in either crossed or uncrossed disparity at random. The subject was not aware of the nature of the disparity to be presented to him. The degree of disparity was kept steady at 1.5 degrees. When a pair of crossed disparate stimuli was presented, a convergence movement was required to fuse the point targets, whereas presentation of targets in uncrossed disparity required a convergence relaxation movement. The subject was instructed to look at the point and to try to keep it single.

In every case in which a convergence movement was called for, it was promptly carried out. One subject also carried out all convergence relaxation movements as required, but the other two showed hesitation when a stimulus to convergence relaxation was given. They made no change in vergence; they began a mild convergence movement after an extremely long reaction time (up to 0.5 second) followed by a divergence movement, or they diverged very slowly after a long interval of inactivity. None of the subjects reported more than a fleeting impression of diplopia, in spite of the fact that their lines of sight were overconverged as much as 1.5 to 2 degrees for seconds at a time.

Since every crossed disparity presentation gave rise to an immediate convergence movement, it is concluded that this experiment verifies the ability of observers to

distinguish crossed from uncrossed disparity that has been demonstrated by psychophysical research. The differences in responses seem to be due to a genuine difference between the mechanism of convergence and that of convergence relaxation.

The second aspect of the problem studied was the time character of convergence and convergence relaxation movements.

A typical record obtained when the object at 135 cm. was replaced by a pair of crossed disparate targets is shown in Figure 2.§ When the disparate targets were again replaced by the single target, records like Figure 3 were obtained.

Figure 2 shows clearly that, although the movement required is a pure vergence movement, since a symmetric stimulus is being presented, small conjugate movements take place during the course of the movement. This is often seen both in convergence and in convergence relaxation responses, although the recording shown in Figure 3 does not happen to exhibit it. The present study is confined to the vergence movements, and hence only the time rate of change of the convergence

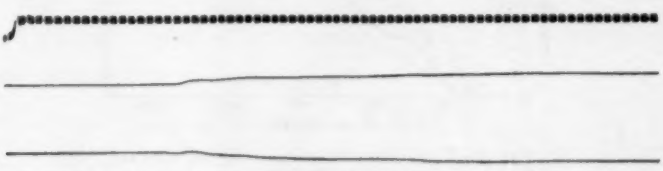

Fig. 2.—Photographic record of eye movement response to a 6-degree convergence stimulus.
The upper line represents the stimulus line. It is interrupted 100 times per second, and its displacement, at the beginning of the record, indicates the instant of presentation of the convergence stimulus.
The middle and lower lines represent the traces of the right and left eyes, respectively. Nasal movement of the right eye is shown as an upward displacement of the middle line. Nasal movement of the left eye is shown as a downward displacement of the lower line. Convergence, the combination of these two movements, is shown in this Figure as a separating of the two lines.

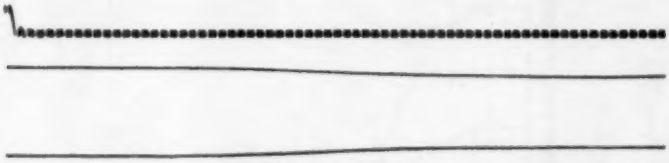

Fig. 3.—Eye movement response to a change of stimulus from 7.5-degree convergence to 1.5-degree convergence (6-degree convergence relaxation movement).
See legend for Figure 2. The approaching of the two traces represents a reduction in the convergence level.

level was analyzed, regardless of any conjugate movement that may have been superimposed on this convergence. The conjugate movements all show the characteristics discussed previously.‖ The superposition of convergence on the saccadic movement may give the appearance of unequal extent of such a movement in the two eyes. When the convergence is factored out, however, the saccadic movements have equal time and displacement characteristics in the two eyes. This is strong evidence for the view that entirely different neurological pathways are involved in the organi-

§ The lenses of the eye movement camera produce an inverted image of all objects on the film. As a consequence, convergence is shown as an increasing separation of the traces on the records.

‖ References 1 and 2.

zation of these two response patterns, these being summated at the level of the motoneurons of the third, fourth, and sixth nerves, which act as final common pathways.

The changes in convergence in movements, such as those illustrated in Figures 2 and 3, are plotted against time in Figures 4 and 5. The movements shown in Figure 4 all started with the eyes binocularly fixating an object requiring a convergence of 1.5 degrees. This object was replaced by a configuration at the same objective distance, which required 3, 4.5, 6, or 7.5 degrees of convergence for it

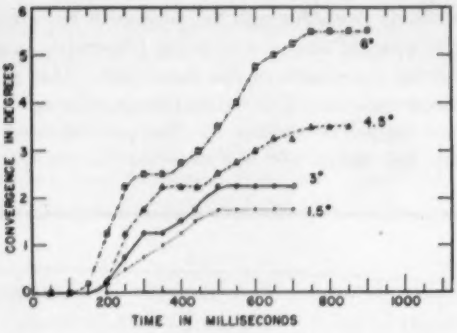

Fig. 4.—Time characteristics of 1.5-, 3-, 4.5-, and 6-degree convergence movements.

The ordinates and the labels of the curves refer to convergence levels relative to that of the screen distance, viz., 1.5 degrees. Stimulus changes occurred at zero time.

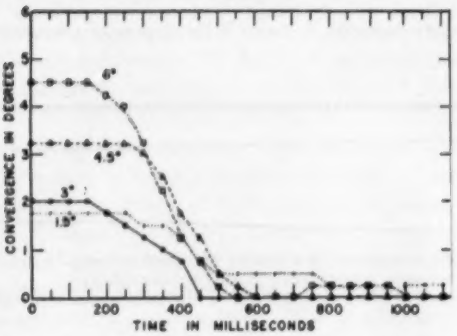

Fig. 5.—Time characteristics of 1.5-, 3-, 4.5-, and 6-degree convergence relaxation movements.

At zero time, disparate spots constituting stimuli for 3, 4.5, 6, and 7.5 degrees of convergence were replaced by a single spot on the screen. The ordinates and the labels of the curve refer to convergence levels relative to that of the screen distance, viz., 1.5 degrees.

to be imaged simultaneously on the foveas of the two eyes. The graph thus illustrates the time characteristics of 1.5-, 3-, 4.5-, and 6-degree convergence movements. Figure 5 shows the time characteristics of the relaxation of convergence from the above-mentioned convergence levels back to the 1.5 degrees of convergence required to fuse the single object on the screen.

Interestingly, the level of convergence reached during the first second after the stimulus presentation often differs by as much as a degree or more from the one required for binocular fixation with the centers of the foveas. Very slow changes in convergence take place in the subsequent few seconds, but they account for only a small fraction of the convergence lag.

The curves show the usual reaction time of 150-200 msec. to a visual stimulus. It was difficult to estimate whether the plateaus in the higher convergence curves

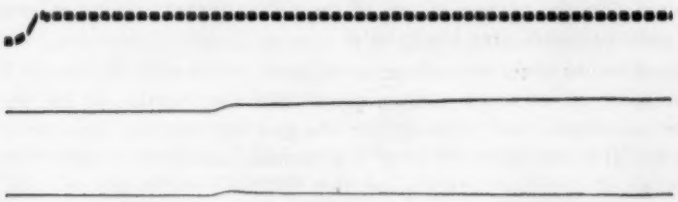

Fig. 6.—Photographic record of eye movement response to an asymmetric convergence stimulus.

See legend of Figure 2 for interpretation of traces on record.

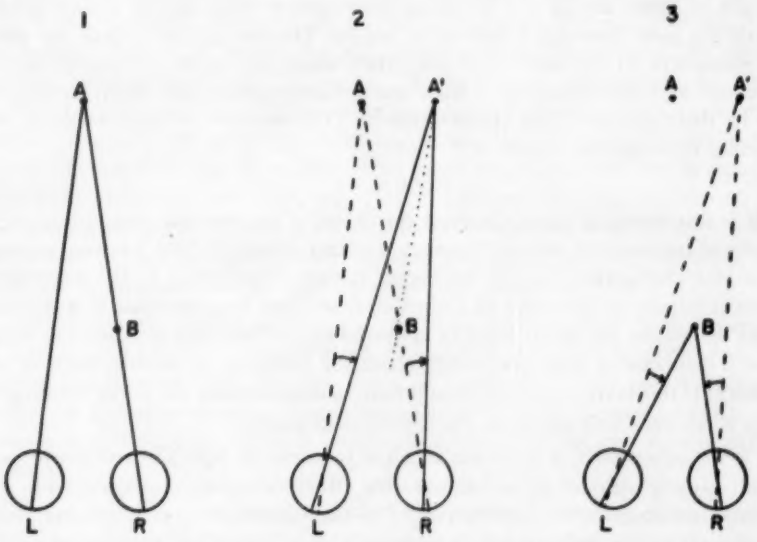

Fig. 7.—Schematic diagrams illustrating sequence of movements in changing fixation from *A* to *B*.

1, binocular fixation of *A*; *2*, conjugate lateral movement without change of convergence to *A'*, so that bisector of angle of convergence passes through *B*; *3*, convergence movement from *A'* to *B*.

Steps 2 and 3 are to some extent superimposed; but, in view of their time characteristics, they are easily distinguished.

represent a complete cessation of convergence for intervals of 100-150 msec. or whether small convergence changes occurred, since the precision with which the convergence could be read off the records (about 0.125 degree) did not permit us to rule out either possibility.

The response marked 1.5° in Figure 5, although it represents a 1.5-degree convergence relaxation, is also typical of the response—if one is seen at all—to a 1.5-degree true divergence stimulus.

Asymmetric convergence was the third aspect of the problem that we investigated. The all-inclusive case of this type of response is the one in which a stimulus change is given such that seemingly the movement of only one eye is required to reestablish binocular fixation. This is the case in which a far and a near object both are situated on a line of sight of one eye, and this situation was simulated in our apparatus by the placing of one of the disparate light points in coincidence with the point originally seen binocularly.

A typical record of the eye movement response to this stimulus change is shown in Figure 6. It constitutes a surprisingly definite confirmation of the thesis that conjugate movements and convergence changes are entirely separate response mechanisms. It is seen that first there is a saccadic movement of the two eyes to a new direction of conjugate lateral gaze such that the bisector of the angle of convergence actually includes the new fixation point. A convergence movement then takes place bringing the lines of sight to intersect in the new fixation point. Far from remaining constant in direction throughout the maneuver, the line of sight of the one eye first swings out in unison with that of the other eye and then is brought in again during the binocular convergence response. It finally assumes exactly the same direction it had at the outset. The two components of the adductive movement of the other eye, viz., that belonging to the conjugate saccadic movement and that belonging to the convergence response, are clearly distinguishable by their different time characteristics. This sequence of movements is schematically illustrated in Figure 7.

COMMENT

It is interesting to speculate about the origin of the diphasic response to higher degrees of convergence stimuli. No such doubling occurs in the 1.5-degree response, but it is a characteristic of all the higher curves. The length of the convergence pauses is roughly of the order of a reaction time. One may postulate that the pause marks the end of the initial burst of convergence and that the fact that the images are still disparate at that time brings about the initiation of another burst of convergence. If this is true, then one would have to conclude that the initial convergence effort is not very well related to the degree of disparity.

On the other hand, it is known that the response to high levels of convergence stimuli usually includes an accommodative effort, which is associated with some degree of accommodative convergence. The total convergence response may under these circumstances be regarded as made up both of accommodative and of fusional convergence. Experiments [7] have shown that with convergence levels of more than about 3 degrees some accommodation, and hence accommodative convergence, is brought into play, even though the object remains at infinity. On this basis the doubling of the convergence curves may be interpreted as showing separate bursts of accommodative and of fusional convergence, which are not brought into play simultaneously. Validation of this interpretation would require a careful investigation of the amount of accommodation and its timing.

Also, attention should be drawn again to the clear differentiation that can be made between vergence movements and conjugate movements. Not only are their time characteristics quite different, but they are brought into play independently.

Occasionally their effects are additive, but with sufficient resolution in the time dimension it is always possible to separate them.

One of the most interesting observations has been the absence of more than a fleeting moment of diplopia following the stimulus change in spite of the fact that often it was almost a second before the convergence approached the required level. This is in accord with a number of findings of Stewart,¶ who observed a consistent lack of correlation between the subjects' reports of diplopia and the actual periods during which the under- or overconvergence exceeded the limit of Panum's areas. Moreover, it was found in the present experiments that the convergence level often deviated by as much as a degree or more from that required for binocular fixation of the object with the center of the foveas. Recent experiments in what is called fixation disparity [8] seem to indicate that subjective measurements of the underconvergence in similar circumstances yield values of no more than a few minutes of arc. Whether this difference is due merely to the difference in the procedure or whether the subjective measurement of the underconvergence differs from objective determinations for more fundamental reasons will have to be settled by further experiments.

SUMMARY

Photographic eye movement records were obtained showing responses to convergence and convergence relaxation stimuli. Objects at a constant distance but with varying degrees of horizontal disparities were presented to three normal observers. Stimuli requiring 1.5 degrees of convergence relaxation and others requiring 1.5 degrees of convergence were presented at random, and no cues other than the nature of the disparity (crossed or uncrossed) were available to the subject. There is always an immediate convergence movement when this is required. Convergence relaxation responses are slower; sometimes no response occurs, and occasionally a tentative response is even made in the opposite direction after a long reaction time. It is concluded that convergence and convergence relaxation stimuli can usually be differentiated, but that the response mechanisms differ.

Convergence movements show a reaction time of about 0.15 to 0.20 second. A 1.5-degree convergence movement takes about 0.4 second to be completed, not including the reaction time. Higher levels of convergence take longer to reach, and show a diphasic response. The final convergence level is often as much as a degree or so less than the stimulus without any reports of diplopia on the part of the subject.

The duration of convergence relaxation movements is inversely proportional to their extent. Small convergence relaxation movements not only are very slow but are often preceded by extremely long reaction times.

Responses to stimuli requiring asymmetric convergence consist of two parts, (*a*) the conjugate saccadic movement, bringing the bisector of the angle of convergence over to include the new fixation point, and (*b*) a convergence movement.

Eye movement records with good time resolution enable conjugate saccadic movements to be clearly differentiated from the slower convergence responses. Small saccadic movements are often superimposed on a long vergence movement,

¶ Stewart, C. R.: A Photographic Investigation of the Lateral Fusional Movements of the Eyes, unpublished Ph.D. dissertation, The Ohio State University, 1951.

and the additivity of the two types of innervation, both using the final common pathways of the third, fourth, and sixth nerve motoneurons, then becomes quite evident.

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Experimental Studies of the Choroidal Vessels

IV. Pharmacologic Observations

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and
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The close interplay existing between the neural transmission and some pharmacologic agents made it advisable to consider together in this section the innervation of the choroid and the action of drugs on the vessels of this structure.*

I. INNERVATION OF THE CHOROID

1. Extrinsic Nerves

The choroid is well provided with branches of the ciliary nerves. These nerves are delicate filaments through which sympathetic, parasympathetic, and sensory fibers reach the eye. In the rabbit the anatomy of the orbital nerves was carefully studied by Peschel.[1]

A. Sympathetic Innervation.—(*a*) Anatomic Data: The preganglionic fibers arise in the rostral thoracic segment of the spinal cord. The white rami communicantes carry the fibers to the cervical sympathetic chain. Here they ascend to the superior cervical ganglion, where they synapse around the postganglionic neurons.

The postganglionic fibers leave the ganglion through the internal carotid nerve, and they pass by the cavernous plexus. Finally the fibers traverse the sympathetic root of the ciliary ganglion and, without relaying, become incorporated in the short ciliary nerves.

Some authors emphasize the importance of the pericarotideal sympathetic plexus for providing nerve filaments to the uvea.

(*b*) Physiologic Data: It is generally accepted that stimulation of the sympathetic fibers leads to constriction of the uveal tract.

In direct observations on rabbits reported by Leber,† the posterior ciliary arteries that run in the choroid contracted after stimulation of the sympathetic. Von Schulten [5] also observed a variable constriction of the arteries after dilatation of the pupil developed. Studies in albino rabbits with a Gullstrand ophthalmoscope were made by Cohen and Bothman.[6] They noticed that stimulation of the central end of the

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* The present investigations were carried out on living albino rabbits. The techniques for observation of the choroidal circulation through the outer ocular coat have been described before.

† References 2-4.

sympathetic produced a constriction of the arteries, with no change in the veins. Greaves and Perkins ‡ reported some contraction of the choriocapillaries after sympathetic stimulation. Their observations were made through dehydrated scleras of albino animals.

Manometric studies on animals made by Henderson and Starling [9] and Wessely,§ and most recently on rabbits in Davson,‖ agree with the view that the sympathetic conveys vasoconstrictor fibers to the vessels of the uvea. Their evidence was drawn indirectly from the observation that sympathetic stimulation caused a decrease in intraocular pressure. Von Sallmann, Meyers, and Pillat [16] also produced a fall in intraocular pressure by electric stimulation of the sympathetic in cats; they are under the impression that epinephrine is the chemical mediator liberated to the effector tissue during stimulation of the supplying nerve. On the basis of experiments on rabbit, Schmerl and Steinberg [17] postulated that stimuli from the diencephalon which travel by way of the superior cervical ganglion contract the capillaries.

Bellarminoff [18] believed that dilator responses are present after stimulation of the sympathetic, in addition to the constrictor effects.

Temporary dilatation of the choroidal vessels in rabbits was reported by Sinitzin [19] and Hertle [20] after excision of the superior cervical ganglion. Jaffe [21] also believed that shortly after sympathectomy there is vasodilatation; after postganglionic sympathectomy and because of the law of denervation, vasoconstriction can occur when the sensitized effector cells are exposed to the normal level of epinephrine.

Adler, Landis, and Jackson [22] could not show any effect of severance of the sympathetic nerves on the intraocular pressure. From this and other experiments, the conclusion has been drawn that the intraocular vessels are little affected by neurogenic tone.[23]

In the present observations, preganglionic electric stimulation ¶ of the intact cervical sympathetic chain of one side for 60 seconds or more evolved only a slight constriction of the long posterior ciliary arteries and moderate pupillary dilatation. Cutting off the nerve did not modify the caliber of the vessels.

B. Parasympathetic Innervation.—(*a*) Anatomic Data: The preganglionic fibers to the ciliary ganglion arise at the midbrain in the Edinger-Westphal nucleus. They traverse the oculomotor nerve, the inferior division of which gives off the short motor root through which they reach the ciliary ganglion. The postganglionic fibers arise in the ganglion and reach the globe by the ciliary nerves.

(*b*) Physiologic Data: Schmerl and Steinberg [17] believed that stimuli of parasympathetic nature travel from the diencephalon by way of the ciliary ganglion and produce vascular dilatation. According to Greaves and Perkins,# neither section nor stimulation of the third cranial pair in rabbits has a significant effect on the intraocular pressure. This is in agreement with the opinion of Adler [23] and others that no vasodilator fibers run to the intraocular vessels, whose stimulation results in a rise of intraocular pressure.

C. Sensory Innervation.—(*a*) Anatomic Data: The different fibers that supply the sensory innervation to the eye are components of the nasociliary branch of the

‡ References 7 and 8.

§ References 10-13.

‖ References 14 and 15.

¶ Pulse frequency, 20/sec.; duty cycle, 0.1 sec. (10%); intensity, 71 volts.

References 7 and 8.

ophthalmic nerve, the first division of the trigeminal nerve. The fibers pass through the long, or sensory, root of the ciliary ganglion, and without synapsis they run in the ciliary nerves.

(*b*) Physiologic Data: Schiff [24] and others reported the development of hyperemia in the rabbit's choroid after section of the trigeminal nerve.

Von Hippel and Grünhagen,[25] Bernard,* Panas,[27] Grünhagen and Jesner,[28] von Schulten,[5] and Bellarminoff [18] assumed that the fifth nerve carries vasodilator fibers to the choroid. Some of these authors arrived at their conclusions because stimulation of the trigeminal gives rise to an increase in intraocular pressure, an effect attributed to excitation of dilator fibers. According to Leber,† the presence of these filaments could never be demonstrated by direct observations. Henderson and Starling [9] also stated that the fifth cranial nerve contains no vasodilator fibers to the eye, and this conclusion remains uncontested up to the present. These authors attributed the opposite results previously described partly to a general rise in blood pressure, owing to stimulation of a sensory nerve, and partly to a contraction of the orbital plain muscle, due to stimulation of the associated sympathetic fibers.

The sensory uveal innervation is important in vascular dynamics because it mediates axon reflexes involving vasodilatation through the liberation of histamine (Magitot,‡ Duke-Elder and Duke-Elder,[31] Moreu,[32] and others).

2. Intrinsic Nerves

Since Saint-Yves [33] first described the choroidal innervation, our knowledge has grown apace, and the subsequent literature may be represented by the contributions of Müller,§ Bietti,[36] Boeke,[37] Rossi,[38] Matteucci,‖ and many others. The two last-mentioned authors have studied and reviewed the subject extensively in recent years.

The choroid is supplied by fibers from the ciliary nerves. These fibers traverse the perichoroidal space and form well-developed plexuses that extend in the inner layers of the suprachoroid and in the vascular strata of the choroid. This network gives origin to the finest branches, which end by small swellings in the musculature of the vessels.

Associated with the plexuses there have been described multipolar ganglionated cells. The presence, connections, and functions of these cells are still a subject of debate.

II. AUTONOMIC NEURAL TRANSMISSION

The question of how nerve impulses cross the intercellular junction has given origin to the humoral theory for the explanation of this mechanism. The theory assumes that the nerve impulse is not transmitted directly to the effector cell, but that it releases substances, called neurohormones by Fredericq,[41] which produce the characteristic response of the cells.

The chief chemical mediators of nerve transmission are acetylcholine and a substance similar to, if not identical with, epinephrine or arterenol; these substances are presumably formed from inactive precursors. In connection with the neurohormones, mention must be made of the true cholinesterase, which destroys acetylcholine, and an amino oxidase or related catalysts, which destroy epinephrine.

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* Bernard, C., in discussion on Veyssiere.[26]

† References 2-4.

‡ References 29 and 30.

§ References 34 and 35.

‖ References 39 and 40.

Some of the best minds in pharmacology have worked on the problem of neural transmission, notably Dale,[42] Loewi,¶ and Cannon and Rosenblueth,# to cite only a few. For review and bibliography in the field of ophthalmology, the works of Van Dyke,[48] Leopold,[41] Scheie,[49] and Swan [50] can best be consulted.

Using the neurohumoral theory of transmission as a background, a classification of the autonomic drugs has been prepared, following the tables of Van Dyke [48] and Leopold.[41]

I. Drugs acting on the autonomic nervous system

1. Peripherally acting agents

A. Drugs acting on the parasympathetic postganglionic elements

(*a*) Drugs acting on effector cells so as to mimic the muscarinic action of acetylcholine (cholinergic drug [51])

*(1) Methacholine chloride

(2) Carbachol

(3) Bethanechol chloride

(4) Pilocarpine nitrate

(*b*) Inhibitors of the enzyme cholinesterase, which normally hydrolyzes the neurohormonal transmitting agent acetylcholine, and which therefore markedly prolongs the action of the locally produced acetylcholine (anticholinesterases; parasympathomimetic drugs)

(5) Physostigmine salicylate

(6) Neostigmine bromide

(7) Isoflurophate (di-isopropyl fluorophosphate)

(*c*) Drugs blocking off cholinergic action at the periphery (peripheral parasympathetic-autonomic-blocking agents; parasympathetic-blocking drugs)

(8) Atropine sulfate

(9) Scopolamine hydrobromide

(10) Methantheline bromide

B. Drugs acting on the sympathetic postganglionic elements

(*a*) Drugs which act on the effector cells so as to mimic the action of the sympathetic neurohumoral transmitter (adrenergic drugs)

(11) Epinephrine hydrochloride

(12) Arterenol bitartrate

(13) Ephedrine sulfate

(14) Phenylephrine hydrochloride

(15) Methoxamine hydrochloride

(*b*) Enzyme inhibitors that prevent the destruction of the neurohumoral transmitter in the sympathetic nerve endings, the locally produced substance having a prolonged effect (sympathomimetic drugs; antioxidase agents)

(16) Cocaine hydrochloride

(*c*) Compounds that specifically inhibit certain responses of effector cells to sympathetic nerve impulses, epinephrine, or related amines (adrenergic-blocking agents; peripheral sympathetic-autonomic-blocking agents).[52]

β-haloalkylamines

(17) Dibenamine

Imidazolines

(18) Tolazoline hydrochloride U. S. P.

(19) Phentolamine methanesulfonate U. S. P.

¶ References 43-45.

References 46 and 47.

* As examples were used the drugs that were tested in the present investigation.

Benzodioxanes

(20) Piperoxan hydrochloride

Ergot alkaloids [53]

Ergotamine group

(21) Ergotamine tartrate

Ergotoxine group

(22) Ergotoxine ethanesulfonate

Ergobasine group

(23) Ergonovine maleate U. S. P.

2. Drugs affecting autonomic ganglia

Agents that interfere with transmission through ganglia, similar to the paralyzing effect of large doses of nicotine (ganglion-blocking agents)

(24) Tetraethylammonium chloride

(25) Hexamethonium chloride

3. Centrally acting agents

Drugs that influence centers in brain, such as medulla or diencephalon, that are superimposed on connector cells of autonomic system

Hypothalamic center responds to cholinergic agents; e. g., acetylcholine, physostigmine, etc., can produce parasympathetic or sympathetic activity, depending on area of hypothalamus stimulated

For example, preoptic region—parasympathetic response

postchiasmal region—sympathetic response

Cerebral cortex also responds to acetylcholine and physostigmine.

II. Directly acting agents

1. Vasodilators

(26) Nicotinic acid

(27) Aminophylline

(28) Amyl nitrite

(29) Glyceryl trinitrate

(30) Ether

2. Vasoconstrictors

(31) Histamine phosphate

(32) Vasopressin

(33) Barium chloride

(34) Croton oil

Each one of these agents was tried at least in three different animals in various concentrations. Observations on proptosed eyes of rabbits were usually restricted to a lapse varying from 30 to 60 minutes after administration of the drug. This limitation was imposed by the marked changes that develop in the eye due to prolonged exposure.

Cholinergic Drugs and Muscarinic Action [54]

In this section reference to the following drugs will be made: (1) the derivatives of choline, (2) pilocarpine, and (3) the anticholinesterases.

(*a*) *Acetylcholine.*—This is the specific neurohormone liberated by the postganglionic fibers of the (craniosacral) parasympathetic division of the autonomic nervous system; this peripheral action has been termed muscarinic. In addition, acetylcholine acts on all the autonomic ganglia to produce the nicotinic effect and, furthermore, plays an important role in the nervous transmission of the voluntary nervous system.

Acetylcholine itself is unstable and its action brief. The effects of the drug are so manifold that it is of little use in therapeutics, except as a model from which more specialized congeners have been provided by synthesis.

After experiments in intact dogs and perfused dog heads, Colle, Duke-Elder, and Duke-Elder [55] concluded that choline chloride and acetylcholine dilate the minute intraocular vessels. According to von Grolman and Angel [56] and Hara,[57] acetylcholine when injected locally induces a dilatation of the intraocular vessels, which develops immediately after injection.

(*b*) *Methacholine* (acetyl-β-methylcholine; Mecholyl).—This agent is closely related to acetylcholine; it is more stable but somewhat less potent. Methacholine produces practically no nicotinic action and causes strong peripheral vasodilatation, involving most of the blood vessels, with fall of pressure.[58]

According to Scheie,[49] methacholine causes a marked vasodilatation of the conjunctival blood vessels and probably has a similar effect upon the vessels of the uveal tract. Swan and Hart [59] demonstrated that this drug decreases the blood-aqueous barrier in rabbits.

(*c*) *Carbachol* (carbamylcholine; Carcholin; Doryl).—This drug is even more stable than the one previously described, and cholinesterase has only a very feeble destructive action on it; hence anticholinesterase drugs have no effect in potentiating its action. Carbachol produces a marked nicotinic effect on the ganglia that can counteract the initial muscarinic response of vascular dilatation.

It is the opinion of Velhagen [60] and de Sanctis [61] that carbachol produces a vasodilatation of intraocular vessels. Swan and Hart [59] observed in albino rabbits a decrease in the barrier between the blood and the aqueous when this drug was administered.

(*d*) *Bethanechol* U. S. P. (carbamylmethylcholine; Urecholine).—This agent is not destroyed by cholinesterase and has very little nicotinic action.

(*e*) *Pilocarpine*.—Pilocarpine has only muscarinic action; that is, it stimulates directly structures innervated by postganglionic cholingeric nerves. It is not hydrolyzed by cholinesterase. This compound, after intravenous administration into living animals and on perfused blood vessels, has been proved to produce vasodilatation. In man ordinarily very little effect is produced on the circulation in doses which are useful in glandular stimulation.

Pilocarpine, according to Margerin,[62] is a dilator of the peripheral vessels of the head and neck. This vasodilating action was demonstrated by Michael and Vancea [63] and Bailliart and Bidault [64] in the conjunctival vessels. After local instillation of the drug Cristini [65] noticed a dilatation of the iris vessels.

Kadlicky [66] Thiel,† Dieter,[69] and others postulate that pilocarpine has a vasodilator action on the intraocular vessels. This effect is in general considered to be of low degree (Clarke,[70] Sugar [71]). In Duke-Elder's [72] opinion the drug has also a secondary action through contraction of the ciliary muscle: Feeding arteries to the anterior segment of the uveal tract are constricted as they run through the substances of the muscle, and the traction of its fibers on the choroid tends to open out the venous exits maximally, thus aiding the escape of blood.

Contrary to previous opinions, Colombo [73] considers that pilocarpine acts as a vasoconstrictor.

Scotti [74] did not see dilatation in the choroidal vessels after administration of the drug but assumed that such changes may escape observation. Vilstrup ‡ studied injected specimens of rabbits after local instillation of pilocarpine and observed that the drug had no noticeable effect on the caliber of the vessels.

† References 67 and 68.

‡ References 76-77.

(*f*) *Physostigmine.*—This drug operates chiefly by inhibiting the specific cholinesterase that rapidly destroys the acetylcholine in the body. Physostigmine combines with the enzyme and locks it up temporarily; obviously, such an agent can have an effect only as long as some acetylcholine is manufactured by natural processes.

Bailliart [78] observed that local instillation of physostigmine produces a short vasoconstriction, followed by dilatation of the conjunctival vessels. According to Wessely,§ after physostigmine there are constriction of the conjunctival vessels and dilatation of the vessels in the iris and ciliary body. Ulrich,[79] Koellner,[80] Thiel,‖ Dieter,[69] Cristini,[65] and others also reported vasodilatation in the iris after local application of this drug, and Swan and Hart [59] observed a decrease of the blood-aqueous barrier in rabbits.

Colle, Duke-Elder, and Duke-Elder,[55] after manometric studies in dogs (intact animals and perfused heads) with physostigmine (5-10 mg.), concluded that the drug produces capillary dilatation. A similar opinion is held by Adler,[23] and Duke-Elder [72] postulates also a secondary effect through the ciliary muscle, similar to the one ascribed to pilocarpine.

Larsson [81] distinguished two phases after instillation of physostigmine. The first, and short, one is manifested by vascular turgescence, and it is succeeded by decongestion of the vessels in the iris and ciliary body.

Grönholm [82] observed no change in the position of the rabbit's choroid after administration of physostigmine, and Mohr [83] described vermicular movements of the choroidal vessels induced by the use of this drug. According to Laquer,[84] physostigmine produces a constriction of the choroidal vessels.

(*g*) *Neostigmine* (Prostigmin).—This drug has a pharmacologic action similar to that of physostigmine; that is, it inhibits the action of acetylcholinesterase. In rabbits it has been reported to produce transient vasoconstriction,[85] and, according to Perlow,[86] neostigmine acts as a peripheral vasodilator in humans.

(*h*) *Isoflurophate.*—This substance destroys cholinesterase irreversibly. Therefore its administration decreases profoundly the choline acetylase activity of the tissues after a single administration. This activity returns eventually as new esterase is formed. In animal experiments Leopold and Comroe ¶ and von Sallmann and Dillon [89] demonstrated dilatation of the vessels in the anterior segment after local administration of isoflurophate.

Present Investigation.—In our studies, carried out in living animals, the previously described drugs were used, as indicated in Table 1.

No definite change in the caliber of the choroidal vessels was observed when the agents were used in small doses. When the amount of drug administered was increased, systemic effects were induced that had a secondary influence on the choroidal vessels. This was manifested by pallor of the choroid, by decrease in the speed of blood flow, and in some occasions by pulsations of the arteries at the points where they perforate the sclera. At times a standstill of the flow was observed, with what appeared to be a passive decrease in the caliber of the vessels.

Parasympathetic-Blocking Agents

Of the drugs belonging to this group, the following were tested: (1) atropine, (2) scopolamine, and (3) methantheline.

§ References 10-13.
‖ References 67 and 68.
¶ References 87 and 88.

(*a*) *Atropine.*—Atropine does not prevent the formation of acetylcholine by the peripheral postganglionic nerve fiber when it is stimulated, but prevents it from acting on the cell. In moderate doses atropine stimulates the vasoconstrictor center in the medulla, resulting in a peripheral constriction of the vascular bed. With larger doses the blood vessels are dilated because of direct action of the drug.[90]

According to Coccius,[91] Larsson,[81] and others, atropine induces a dilatation in the vessels of the iris. Cristini [65] described a dilatation of the large vessels in the same structure without any corresponding capillary dilatation.

In the opinion of Koellner [80] and Colombo,[73] atropine causes dilatation of intraocular vessels, and Michael and Vancea [63] observed this effect in the conjunctival vessels. Thiel # considered that the drug dilates the arteries, with collapse of the veins.

Colle, Duke-Elder, and Duke-Elder [55] studied the effect of atropine in the intact and perfused heads of dogs (3 mg.) and concluded that it dilates the minute vessels but not the arterioles. Duke-Elder [72] ascribed this effect also to relaxation of the ciliary muscle. The arteries run in the substance of the muscle so that when it is relaxed any constriction to the lumina of the vessels is removed. At the same time,

TABLE 1.—*Effects of Cholinergic Drugs and Anticholinesterases*

Drug	Route of Administration	Maximal Dose Administered
Methacholine chloride	Intravenous	1 mg./kg.
Carbachol	Local	3% solution
	Intravenous	0.2 mg./kg.
Bethanechol chloride	Intravenous	1 mg./kg.
Pilocarpine nitrate	Local	2% solution
	Intravenous	20 mg./kg.
Physostigmine salicylate	Local	1% solution
	Intravenous	0.5 mg./kg.
Neostigmine bromide	Intravenous	200 mg./kg.
Isoflurophate	Local	0.1% solution

the absence of traction on the choroid allows the vessels of this venous reservoir to collapse, thus tending to encourage stasis; this effect when continued favors engorgement. According to Adler,[28] there is evidence that atropine makes the intraocular blood vessels less permeable to protein.

Contrary to some previous opinions, Dieter [69] and Bailliart and Bidault [64] postulated that atropine acts as a vasoconstrictor. Schneller [92] and Laquer [84] reported dilatation of the choroidal vessels after administration of atropine. The validity of these observations was questioned by Memorsky and Leber.*

(*b*) *Scopolamine.*—This drug has a mechanism of action similar to that of atropine. Ernst [93] and Kochmann [94] considered that scopolamine has a dual effect: It induces vasodilatation when acting directly on the isolated vessels and has also a strong vasoconstrictor effect secondary to central stimulation. According to Walter,[95] scopolamine produces a constriction of the ocular vessels.

(*c*) *Methantheline* (Banthine).—This drug has a anticholinergic, atropine-like action. In addition to this effect, it has been shown to block ganglionic transmission in both the sympathetic and the parasympathetic system.†

References 67 and 68.
* References 2-4.
† References 96 and 97.

Present Investigation.—In the observations undertaken to study the action of these drugs on the choroidal vessels, the drugs indicated in Table 2 were used.

No changes in the choroidal vessels could be ascribed directly to the action of these agents. When given in maximal amounts, the drugs produced a decrease in blood flow with choroidal pallor, arterial pulsations, reversal of circulation, and passive decrease in vessel caliber. These vascular modifications appeared to be secondary to the systemic effects of the drugs.

Adrenergic and Sympathomimetic Drugs

These drugs include a group of agents which stimulate effector mechanisms that are normally under the control of sympathetic nerves.

(*a*) *Epinephrine.*—The outstanding effect of epinephrine is the production of vasoconstriction, which causes a rise in blood pressure. The reaction of different vessels to this drug varies quantitatively and sometimes qualitatively, depending on the susceptibility of the experimental animals. The response of the choroidal vessels to epinephrine appears confusing, partly because its action is not very strong, and is therefore easily complicated by indirect effects and by differences in experimental methods. Also to be considered is that mixtures of epinephrine and arterenol were used in some investigations.

Table 2.—*Action of Parasympathetic-Blocking Drugs*

Drug	Route of Administration	Maximal Dose Administered
Atropine sulfate	Local	2% solution
	Intravenous	10 mg./kg.
Scopolamine hydrobromide	Local	2% solution
	Intravenous	10 mg./kg.
Methantheline bromide	Intravenous	6 mg./kg.

The conclusion arrived at by early observers who studied the actions of epinephrine is that the response of the choroidal vessels to the drug varies according to the preponderance of the local or general effect on the blood vessels (Parsons,[98] Henderson and Starling,[9] Wessely ‡). In anesthetized dogs epinephrine injected in small doses produced a rise in the blood pressure and the uveal vessel caliber increased passively; with large doses the local vasoconstriction asserted itself as the predominant factor. A vasoconstrictor effect was also discerned when the drug was injected directly into the carotid artery.

In artificially perfused eyes smaller doses (10γ) dilated the capillaries, and larger doses (100γ) constricted the arterioles and capillaries (Colle, Duke-Elder, and Duker-Elder [55]).

Studying the effect of minimal physiological amounts of epinephrine in cats (0.1γ to 1.6γ per kilogram), von Sallmann, Meyers, and Pillat [16] found a biphasic response of the blood pressure that was reflected in the intraocular pressure, with the fall in the pressures as the predominant feature. They assumed that the intraocular arteries do not contract sufficiently to prevent a dilatation of the capillary bed as a result of increased blood pressure and that the fall in blood pressure overcompensates for the effect of local vasodilatation. They also postulated some action of epinephrine on the intraocular veins. For an interesting discussion on the effects of

‡ References 10-13.

epinephrine on the cardiovascular tree, the works of Barcroft [99] and Lands and co-workers [100] may be consulted.

Hara [87] injected epinephrine subconjunctivally and observed that the curve of intraocular pressure showed changes corresponding to those which occur in blood vessels of other parts of the body when they contract.

In injected choroidal casts of rabbits, Vilstrup § could not see any change in the size of the capillary lumina either after local instillation of epinephrine (0.2% solution) or after intravitreal injection. The arterioles appeared to be slightly constricted in these studies.

Observations through the pupil of albino rabbits were made by Cohen and Bothman.[6] After intravenous injection of epinephrine (100γ-200γ), they noticed a marked constriction of the choroidal arteries, followed in a few seconds by dilatation.

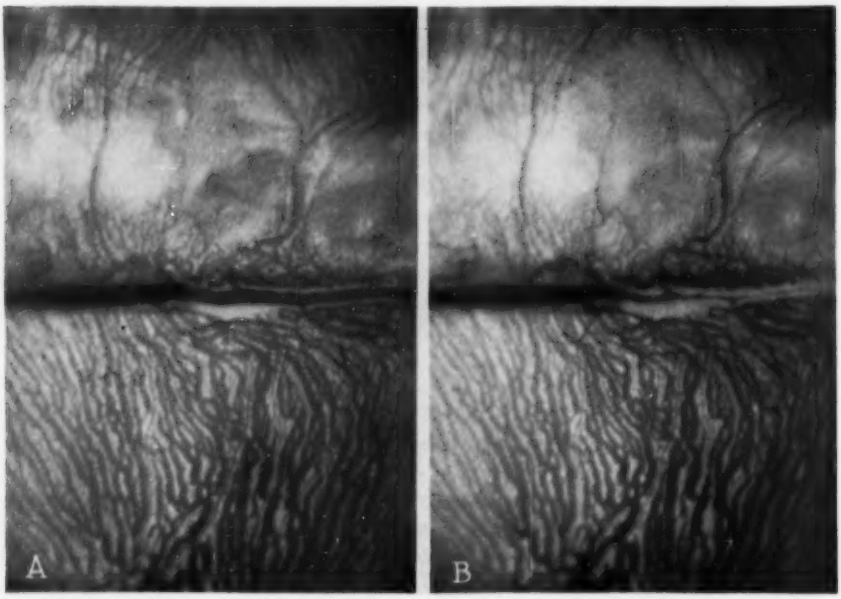

Fig. 1.—Effect of local instillation of epinephrine on the caliber of the choroidal vessels: *A*, before instillation. *B*, after instillation the intraocular portion of the long posterior ciliary arteries has become narrow and tortuous. Reduced to 54% of mag. × 40.

The veins widened immediately after injection. Zwiauer and Bornschein [101] noticed pallor of the fundus but could detect no real contraction of the choroidal vessels following large doses of epinephrine that killed the rabbits. Smaller doses and retrobulbar injections had no definite effect.

Through the dehydrated sclera of living rabbits Greaves and Perkins ‖ observed some contraction of the choriocapillaries after intravenous injection of epinephrine (20γ-200γ).

Present Investigation: Local application of epinephrine hydrochloride (1% solution) induced moderate constriction of the long posterior ciliary arteries. The reduction in caliber developed within one minute after instillation and was more

§ References 75-77.

‖ References 7 and 8.

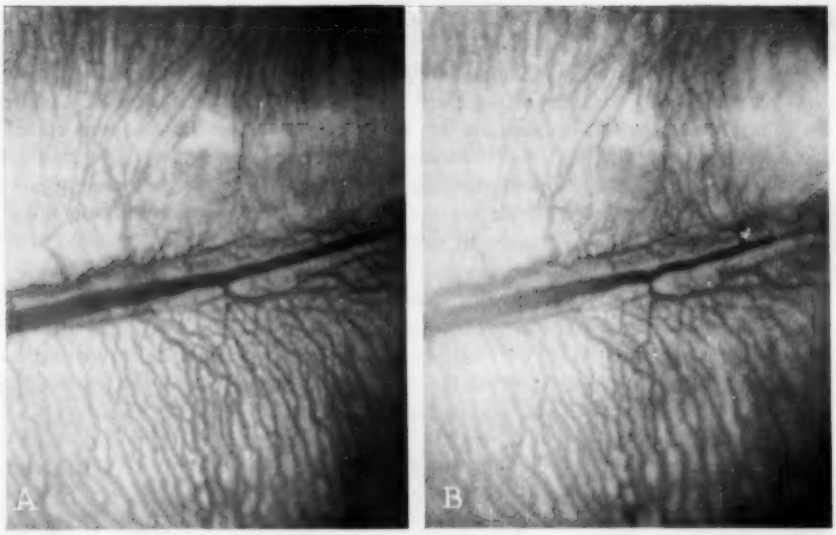

Fig. 2.—Effect of an intravenous injection of epinephrine on the caliber of the choroidal vessels. *A*, before injection. *B*, after injection the distal portion of the long posterior ciliary arteries shows moderate narrowing and tortuosity. Reduced to 68% of mag. × 10.

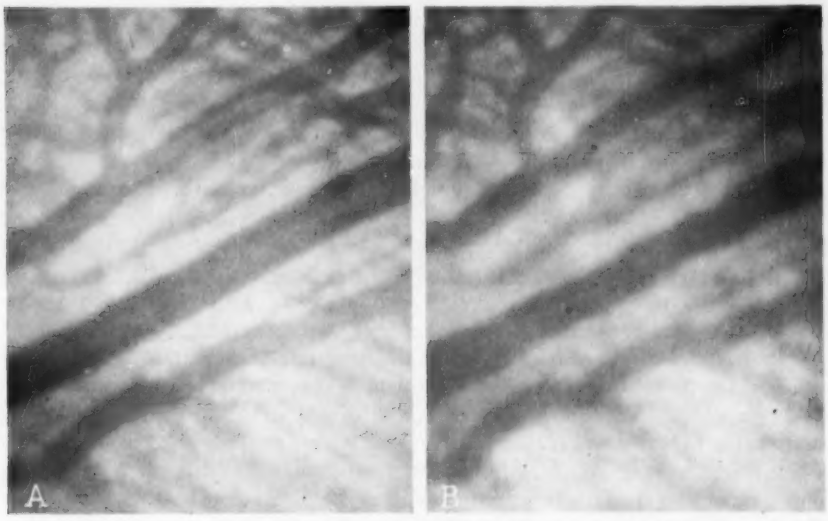

Fig. 3.—Effect of an intravenous injection of epinephrine seen under higher magnification. *A*, before injection; *B*, after injection. Reduced to 68% of mag. × 40.

noticeable in the intraocular portion of the vessel. There was also a slight constriction of the short posterior ciliary arteries. The constrictive effect was focal in type and gave a tortuous appearance to the vessel (Fig. 1). The pupil during these studies became widely dilated.

Intravenous injection of epinephrine (200γ-350γ per kilogram) induced the same general changes as those previously described except that the decrease in vessel

caliber was less pronounced (Figs. 2 and 3). With smaller doses no changes were noticed.

An interesting phenomenon noted frequently after repeated intravenous injections of epinephrine was the passage of white masses through the vessels, more frequently in the veins. These clumps are carried along in the circulation as emboli that seem quite soft and pliable. When large clumps are present, they may plug the venules temporarily and gradually, and, after molding and changing their configuration, slide along until they reach large vessels and are carried away in the circulation. A similar occurrence was occasionally noticed after the use of arterenol and after local trauma to the eye.

After intravitreal injection of epinephrine (1 mg.) a slight constriction developed slowly in the intraocular portion of the long ciliary arteries.

(*b*) *Arterenol.*—After Bacq [102] suggested that arterenol might be sympathin E, von Euler ¶ actually identified this drug as the pressor sympathomimetic substance which he had found in tissues. The existence of two adrenergic transmitters with different actions on the general circulation was postulated by Goldenberg and co-workers.# They considered that epinephrine acts as an over-all cardioaccelerator and vasodilator, whereas arterenol functions as an over-all vasoconstrictor. According to Lands,[108] the differences in response to the drugs are quantitative rather than qualitative.

Burn and Hutcheon [109] and von Euler ¶ have arrived at the conclusion that arterenol is the predominant chemical transmitter in the sympathetic nervous system of the cat, whereas Gaddum and Kwiatkowski * identified epinephrine as the transmitting agent in the ear of the rabbit.

In anesthetized cats, von Sallmann, Meyers, and Pillat [16] demonstrated that arterenol (0.1γ to 1.6γ per kilogram), when administered by the intravenous route, produces a rise in intraocular pressure. They assume that the intraocular arteries do not contract sufficiently to prevent a dilatation of the capillary bed as a result of increased blood pressure.

Present Investigation: During our observation of the choroidal circulation in the proptosed eyes of rabbits, intravenous administration of arterenol bitartrate (10γ-15γ per kilogram) produced a slight to moderate focal type of constriction of the intraocular portion of the long posterior ciliary arteries (Fig. 4).

Local instillation of arterenol (0.01% solution) induced a persistent and moderate constriction of the same vessels.

(*c*) *Ephedrine.*—Ephedrine produces vascular effects similar to those of epinephrine, but the dilatation phenomenon usually is absent. The resemblance between these drugs suggested an identical mechanism of action, but this appears partially contradicted by some observations. Ephedrine enhances the results of stimulation of the postganglionic sympathetic neuron, even though the drug is present in a concentration too small to be effective by itself; thus, much of the vasoconstrictor effect of ephedrine depends upon its ability to inhibit the destruction of the sympathetic neurohormone. In this sense, it serves the dual purpose of being adrenergic and sympathomimetic.

The vasoconstrictor action of ephedrine was studied by Hou [112] in chambers of the rabbit's ear. These observations showed that within therapeutic doses the drug contracts the arteries but not the smaller vessels.

¶ References 103-105.

References 106 and 107.

* References 110 and 111.

Our Studies: After intravenous administration of ephedrine sulfate (20 mg. per kilogram) slight arterial constriction was observed. The reduction in vessel caliber was evident in the intraocular portion of the long posterior ciliary arteries and was further increased when followed by epinephrine.

(*d*) *Phenylephrine* (Neo-Synephrine).—According to Tainter,[113] phenylephrine is 20 times weaker than epinephrine in its ability to constrict the vascular tree. DuPont Guerry [114] found that phenylephrine produces a lowering of intraocular pressure, and Sugar [71] recommends its use to counteract the vasodilatation induced by isoflurophate in the intraocular vessels.

Our Studies: When applied locally to the proptosed eyes of rabbits, phenylephrine hydrochloride (10% solution) produced a moderate constriction of the long posterior ciliary arteries during their passage through the suprachoroidal space. The

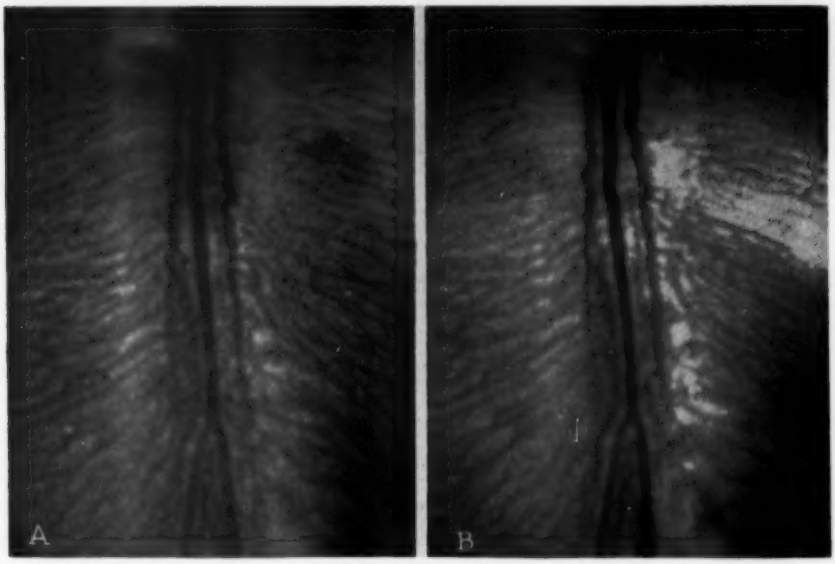

Fig. 4.—Effect of an intravenous injection of arterenol on the caliber of the choroidal vessels. *A*, before injection. *B*, after injection the long posterior ciliary arteries appear slightly narrowed. Reduced to 57% of mag. × 10.

constriction appeared a few minutes after instillation and subsided gradually (Fig. 5). Moderate to marked pupillary dilatation developed slowly.

(*e*) *Methoxamine* (Vasoxyl).—This amine has a pressor action, which appears to be due primarily to peripheral vasoconstriction.†

Our Studies: In living rabbits, methoxamine hydrochloride, when given intravenously (5γ-10γ per kilogram), induced a slight focal vasoconstriction of the intraocular portion of the long posterior ciliary arteries. Smaller doses were without effect, and the observations in general were difficult because the animals developed ocular and generalized involuntary movements. Local instillation (2% solution) produced a wide mydriasis in rabbits but in humans acted as a feeble dilator of the pupil.

† References 115 and 116.

(*f*) *Cocaine.*—Cocaine is considered to be a sympathomimetic agent. This means that it probably does not have a direct stimulating effect, but it blocks the destruction by the oxidases of the locally released sympathetic neurohormone. Another explanation suggests that cocaine might increase the permeability of the muscle cell to sympathin, permitting these cells to be stimulated by much smaller amounts of the hormone.

According to Sollmann,[85] cocaine when applied to the conjunctiva produces local constriction [117] that extends to the iris. This is in agreement with Dieter's [69] view, who considered that this drug acts as a vasoconstrictor of intraocular vessels. Opposed to this are the opinions of Koellner [80] and Colombo,[73] who ascribed to cocaine a dilator effect on ocular vessels.

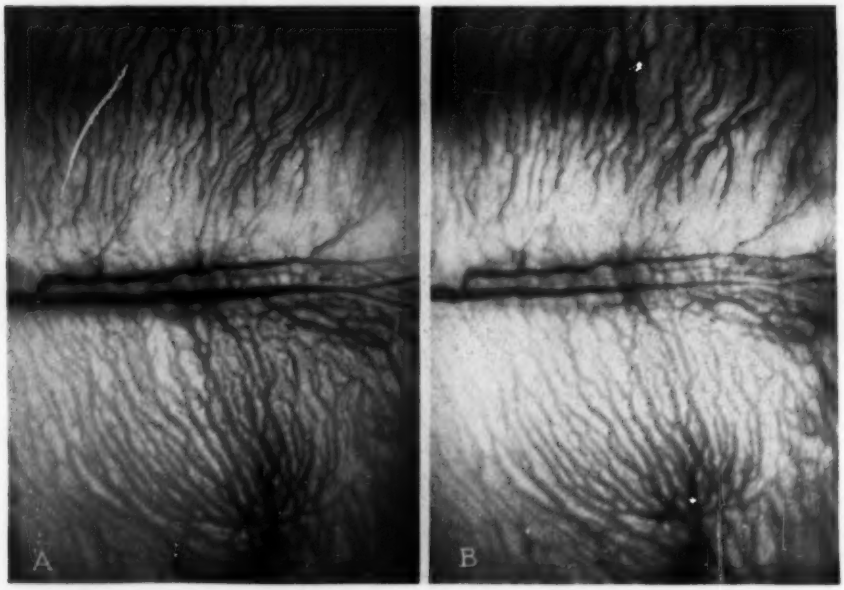

Fig. 5.—Effect of local instillation of phenylephrine on the caliber of the choroidal vessels. *A*, before instillation. *B*, after instillation there is narrowing of the long posterior ciliary arteries, particularly along the area before the division into the two terminal branches. Reduced to 54% of mag. × 10.

Present Investigation: Cocaine hydrochloride was used locally (4% solution) without producing significant changes in the caliber of the choroidal vessels.

Adrenergic- and Sympathetic-Blocking Agents

A widely used terminology of these drugs is based on the opinion that (1) adrenergic-blocking agents (adrenolytic, or antiadrenergic substances) block the effect of epinephrine and its congeners on the cells, while (2) sympathetic-blocking agents (sympatholytic, or antineuradrenergic substances) block the response to stimulation of the sympathetic nerves. There are authors that doubt the wisdom of some of the terms previously referred to.

(*a*) *Dibenamine* (N,N-dibenzyl-β-chloroethylamine hydrochoride).—This is a drug related to the nitrogen mustards that possesses potent adrenolytic and sym-

patholytic effects.[118] According to the experiments of DeLong and Scheie,[119] there is no indication that Dibenamine produces a significant effect upon the blood-aqueous barrier.

(*b*) *Tolazoline* (Priscoline).—This agent also exhibits adrenolytic and sympatholytic properties. Rogers [120] and others have reported dilatation of the peripheral vessels after its administration. The mode of this peripheral vasodilatation is secondary to autonomic blockade, and an important direct action on the vessels has been suggested.

(*c*) *Phentolamine* (Regitine).—This drug has a sympatholytic dose that is 30 times the adrenolytic dose.[121] Phentolamine is capable of converting the vasoconstricting effects of epinephrine into a vasodilating effect, and, according to Green and Grimsley,[122] the drug is able to produce cutaneous vasodilatation in man and animal.

(*d*) *Piperoxan* (Benodaine).—Piperoxan acts peripherally on the sympathetic nervous system, and its sympatholytic dose is 40 to 80 times that of the adrenolytic amounts.[123] The agent also exerts a direct constrictor action on peripheral and coronary vessels.[52]

TABLE 3.—*Action of Adrenergic- and Sympathetic-Blocking Agents*

Drug	Route of Administration	Maximal Dose Administered, Mg./Kg.
Dibenamine	Intravenous	25
Tolazoline hydrochloride	Intravenous	25
Phentolamine methanesulfonate	Intravenous	5
Piperoxan hydrochloride	Intravenous	5
Ergotamine tartrate	Intravenous	2
Ergotoxine ethanesulfonate	Intravenous	2
Ergonovine maleate	Intravenous	2

(*e*) *Ergot Alkaloids* (ergotamine, ergotoxine, and ergonovine).—Ergotamine and ergotoxine are chiefly responsible for the epinephrine reversal manifested by the extracts of ergot. Ergonovine has only little adrenergic-blocking action.

All these alkaloids exert a direct constrictive effect on the arteries.[59]

Cohen and Bothman [6] reported that ergot does not produce changes in the choroidal vessels after systemic administration.

Present Investigation.—Represented in Table 3 is the manner in which the previously described drugs were used.

No change in the choroidal vessels could be directly attributed to the action of these drugs; when vascular effects developed, they appeared to be secondary to the systemic modifications induced by the agents. The changes in the choroidal vessels were manifested primarily by pallor of the vascular coat, arterial pulsations, and diminution in the speed of blood flow, with occasional reversal of circulation and passive narrowing of the vessels.

GANGLION-BLOCKING AGENTS

Two of these ganglioplegic drugs were tested, tetraethylammonium and hexamethonium.

(*a*) *Tetraethylammonium* (Etamon, TEA).—This drug is a quaternary ammonium compound and has been shown to block reversibly the transmission of sympa-

thetic and parasympathetic impulses through autonomic ganglia. Tetraethylammonium is considered to be a very potent vasodilator because of its property of interrupting sympathetic stimuli, with release of vasoconstrictor tone.[124]

(*b*) *Hexamethonium.*—This drug has been shown to inhibit the transmission of impulses through all autonomic ganglia, parasympathetic as well as sympathetic. Burt and Graham [125] reported dilatation of the choroidal vessels after the administration of hexamethonium.

Present Investigation.—Table 4 indicates the manner in which these agents were used to study their effects on the choroidal vessels of albino rabbits.

The only changes observed in the vessels of the choroid appear to be secondary to the systemic effects induced by the drug. They consist in a reduction of the blood flow, accompanied by discoloration of the choroid, arterial pulsations, and narrowing of vessel caliber.

Vasodilators

Included in this group of agents are those drugs that increase the vessel caliber, acting directly upon the smooth muscle in the walls of vessels.

(*a*) *Nicotinic Acid* U. S. P. (niacin).—According to Abramson, Katzenstein, and Senior,[126] and others, this drug produces peripheral vasodilatation. Aguilar [127] reported a secondary decrease in intraocular pressure accompanying the peripheral effect of nicotinic acid.

Table 4.—*Action of Ganglion-Blocking Agents*

Drug	Route of Administration	Maximal Dose Administered, Mg./Kg.
Tetraethylammonium chloride	Intravenous	25
Hexamethonium chloride	Intravenous	10

(*b*) *Aminophylline* (theophylline ethylenediamine).—Aminophylline produces vasodilatation by inducing relaxation of the smooth muscles in the vascular wall.

(*c*) *Nitrites* (amyl nitrite and glyceryl trinitrate [nitroglycerine]).—The outstanding action of drugs such as amyl nitrite and glyceryl trinitrate is the rapid and widespread dilatation of the peripheral vascular tree. Although much is said in the literature about dilatation of the arterioles, actually it is the capillaries and venules, according to Salter,[54] which are most susceptible to this group of agents.

Wessely ‡ believes that amyl nitrite dilates intraocular vessels. Zwiauer and Bornschein [101] found no change in the diameter of the choroidal vessels after the administration of amyl nitrite or glyceryl trinitrate to albino rabbits. In the same animals Cohen and Bothman [6] reported dilatation of the arteries and blanching of the veins when glyceryl trinitrate was given.

(*d*) *Ether.*—During ether anesthesia the cutaneous and cerebral vessels are dilated, while the intestinal ones are constricted.[85]

The effect of this agent in relation to the choroidal vessels was considered in the section on anesthesia.

Present Investigation.—The vasodilator agents were tested for their effect on the choroidal vessels, following the arrangement indicated in Table 5.

‡ References 10-13.

Modifications in the choroidal vessels appeared only when systemic effects were evident. The vessels showed a narrowing of their caliber and a gradual slowing of blood flow; choroidal pallor and arterial pulsations were also evident.

Vasoconstrictors

In this group are included drugs that have some constrictor effect. This action is directly upon the wall of the blood vessels and is independent of the autonomic nervous system.

(*a*) *Histamine.*—The susceptibility of the vascular tree to histamine varies in the different animal species.

Excised arteries are constricted by histamine in all species and in nearly all situations.[85] In the dog and monkey, and probably in man under conditions of natural circulation, the action of histamine on the arterial tree may be pictured in general terms as consisting of a constrictor effect on the more central part of the vascular tree (e. g., near the heart), changing to a dilator effect, which is recognizable before the smallest macroscopic arteries are reached. In the cat, the latter vessels are constricted, while a dilator action takes place at some more peripheral point in the arterial bed. In rodents the constricting effect upon systemic arteriolar walls is the predominant response.§

Table 5.—*Action of Vasodilator Drugs*

Drug	Route of Administration	Maximal Dose Administered
Nicotinic acid	Intravenous	30 mg./kg.
Aminophylline	Intravenous	100 mg./kg.
Amyl nitrite	Inhalation	0.2 cc./kg.
Glyceryl trinitrate	Local	3 mg. in solution

The action of histamine on the capillary network of mammals is sometimes manifested by a momentary constriction, but the definite action is wide dilatation of the capillaries. The effect is noted to be widespread in all organs and throughout the animal kingdom.[84]

Cole, Duke-Elder, and Duke-Elder [55] studied the action of histamine on the intraocular vessels. In dogs and cats they found that systemic administration of histamine (5γ-100γ) dilates the minute vessels provided they have sufficient tone; otherwise its action is confined to constriction of the arterioles. In rabbits there was absence of any noteworthy dilator effect; only a slight constriction was noted.

Vilstrup ‖ studied the effect of local instillation of histamine (0.1% solution) in extirpated plastic-injected choroid vessels. She observed a distinct dilatation of all the choriocapillary endothelial tubes; the arterial terminal branches were also dilated, and the venules were markedly increased in caliber. The large veins and the vorticose ampullas were considerably congested and distended. The arteries showed a dubious dilatation.

Present Investigation: Histamine phosphate was administered through different routes. Local application (0.1% solution) was followed by a moderate to marked uniform vasoconstriction of the long and short posterior ciliary arteries (Figs. 6 and 7). The effect was already noticeable 30 seconds after instillation and was particularly evident in the intraocular portion of the long ciliary arteries.

§ References 129-131.

‖ References 75-77.

Intravenous administration of this drug (0.5-1 mg. per kilogram) yielded changes similar to those previously described. They became evident during the injection (Fig. 8).

Intravitreal injection of histamine (0.3 mg.) produced a moderate constriction of the intraocular portion of the long ciliary and the short ciliary arteries. The effect

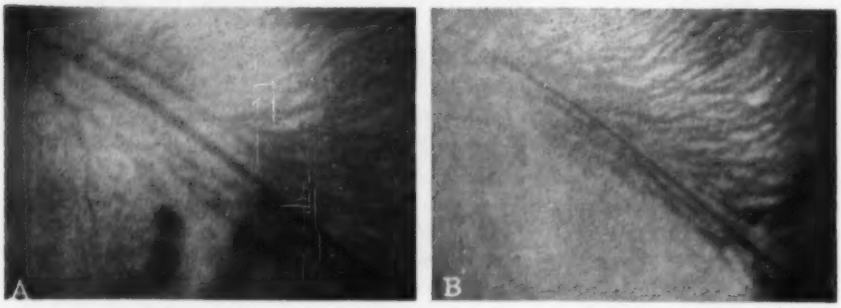

Fig. 6.—Effect of local instillation of histamine on the caliber of the choroidal vessels. *A*, before instillation. *B*, after instillation the long posterior ciliary arteries reveal a marked uniform constriction, while the short ciliary arteries are only moderately reduced in caliber. Reduced to 68% of mag. × 10.

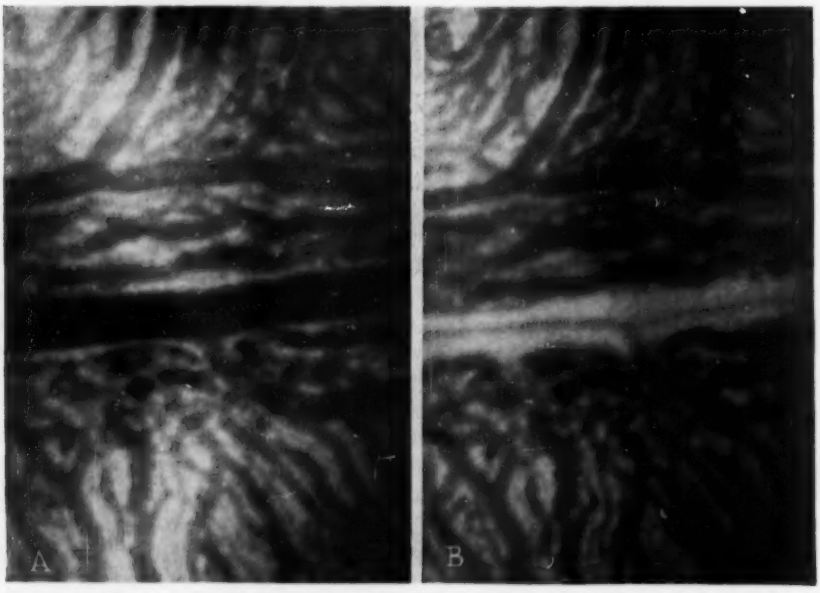

Fig. 7.—Effect of local instillation of histamine seen under higher magnification. *A*, before instillation; *B*, after instillation. Reduced to 57% of mag. × 40.

was slow in appearing, probably because of the time required for the drug to diffuse and to come in contact with the vessels.

(*b*) *Vasopressin* (Pitressin).—This is a pituitary extract that contains the pressor-oliguric fraction of the posterior lobe of the pituitary gland. It has a vasoconstrictor action that occurs in perfused organs and excised arterial segments.[85]

According to Colle, Duke-Elder, and Duke-Elder [55] posterior pituitary U. S. P. (Pituitrin) (3-5 units) in anesthetized intact dogs and perfused heads of the same animals produces a prolonged vasoconstriction of the intraocular vessels. This decrease in vascular caliber is relatively slow in onset and is overcome by the influence of the rise in the systemic blood pressure.

Cohen and Bothman [6] studied the action of posterior pituitary U. S. P. on the choroidal vessels of albino rabbits and did not observe any change in the vascular structures. In the same animals, Zwiauer and Bornschein [101] noticed pallor of the fundus after intravenous administration of vasopressin (8-10 units). No change in vascular caliber was actually seen.

Present Investigation: The local and systemic effects of vasopressin were studied. When applied locally, the drug (10-20 units) produced constriction of the

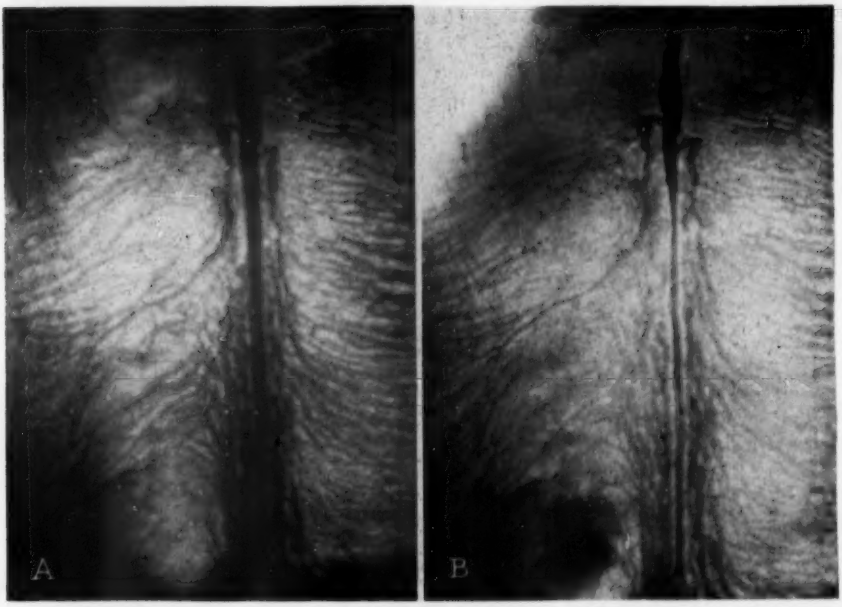

Fig. 8.—Effect of an intravenous injection of histamine on the caliber of the choroidal vessels. *A*, before injection. *B*, after injection there is a moderate uniform constriction in the intraocular portion of the long posterior ciliary artery. Reduced to 57% of mag. × 10.

long and short posterior ciliary arteries that was evident within one minute after instillation. The vasoconstriction is focal in type, and the portions between the narrowed areas acquire a fusiform appearance (Fig. 9).

After intravenous administration vasopressin (3-10 units per kilogram) induced a constriction in all the choroidal arteries. This decrease in vessel caliber was particularly evident in the choroidal arterioles, which in some areas practically became invisible (Fig. 10). It is important to note that this was the only drug to produce a response of such nature in the vessels of the choroid. The vascular narrowing appeared during the administration of the drug and started to subside in a few minutes, and after 20 to 30 minutes the vessels had regained their normal caliber.

(*c*) *Barium.*—This drug produces a strong vasoconstriction by direct stimulation of the arterial muscle and involves all arteries regardless of their innervation.[88]

Present Studies: Barium chloride was administered intravenously to rabbits in doses up to 10 mg. per kilogram. No direct effect of the drug on the choroidal vessels was detected.

(*d*) *Croton Oil.*—This agent when applied locally produces a strong irritation, a property that has been frequently utilized for the study of inflammatory phenomena.

Present Investigation: Local instillation of croton oil (0.05 cc.) to the proptosed eyes of albino rabbits produced a moderate vasoconstriction of the long and short posterior ciliary arteries (Fig. 11). The constrictive effect developed slowly, being apparent within 3 to 5 minutes and reaching its peak after 15 minutes.

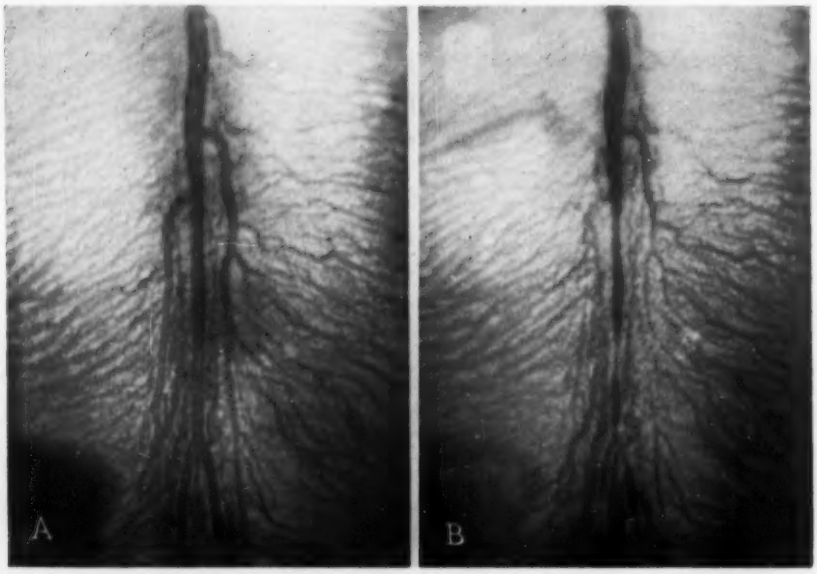

Fig. 9.—Effect of local instillation of vasopressin on the caliber of the choroidal vessels. *A*, before instillation. *B*, after instillation there is a focal type of constriction in the intraocular portion of the long posterior ciliary artery, and the segments between the constricted areas acquire a fusiform appearance. Reduced to 58% of mag. × 10.

Comment.—In discussing the neuropharmacologic studies described in the present section, it is convenient to refer separately to the main vascular responses produced by the different agents.

Vasoconstriction: The vasoconstrictors tested usually induced in the choroidal arteries a response similar to the one observed in other vascular areas. Two special points should be emphasized:

(*a*) First, the dose required to elicit the choroidal vascular response was considerably higher than the dose necessary to cause similar response in other vessels. This was due partially to the experimental conditions, which may have decreased the sensitivity of the ocular vessels studied.

(*b*) Second, the area that became constricted more readily was the intraocular portion of the long posterior ciliary arteries (an exception to this was the intravenous administration of vasopressin, which constricted primarily the choroidal arterioles).

According to Fortin,¶ Duke-Elder,[72] and others, the intraocular portion of the long posterior ciliary arteries has been considered to play an important part in influencing the intraocular pressure after the administration of drugs. These authors are of the opinion that the vascular changes are secondary to the effect of the drug on the ciliary muscle: Vessels that run in the substances of the muscle have their lumen constricted when the muscle contracts and their caliber increases with ciliary relaxation. In the rabbit, the ciliary muscle is poorly developed, and it was observed that the vascular response appeared rapidly and long before any change in pupillary size (and probably in ciliary action) was manifested. Thus, the effect of the drugs appeared to be direct on the vessel, and not secondary to their action on the ciliary muscle.

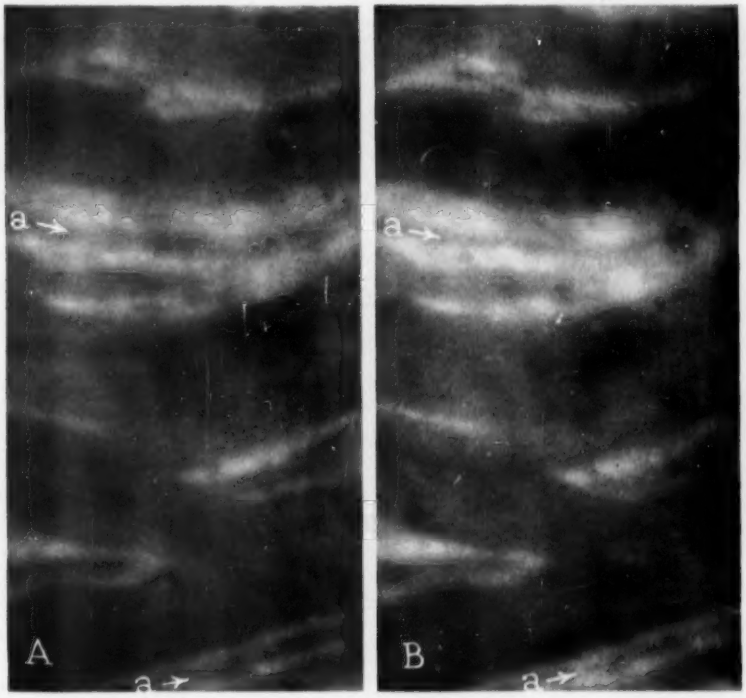

Fig. 10.—Effect of intravenous injection of vasopressin on the caliber of the choroidal vessels. *A*, before injection. *B*, after injection the thinner arterioles (*a*) appear constricted, while the thicker veins do not change their caliber. Reduced to 76% of mag. × 75.

Of particular interest were the white emboli that were observed after trauma and after the administration of some constrictors (epinephrine and arterenol). The importance of white thrombosis and embolism has been recognized in both clinical # and experimental studies.* The latter was covered thoroughly by Lutz, Fulton, and Akers [142] through cinephotomicroscopy in the transilluminated cheek pouch of the hamster. They observed that the white emboli were composed largely of platelets, although mixed emboli of leucocytes and thrombocytes were also observed.

¶ References 131 and 132.
# References 133-135.
* References 136-141.

Vasodilatation: With the vasodilators two general patterns of vascular behavior were evident:

(*a*) When the vasodilators were administered in small doses and no systemic manifestations were observed, we were unable to perceive any change in vessel caliber.

(*b*) Administration of higher doses of vasodilators which interfere with the vital functions of the animal induced a pallor of the choroid, accompanied by a decrease in the speed of flow, and on occasions by intermittent pulsations of the arteries at the points where they perforate the sclera. Sometimes a short standstill of the blood flow was observed, followed by a temporal reversal of the circulation with what

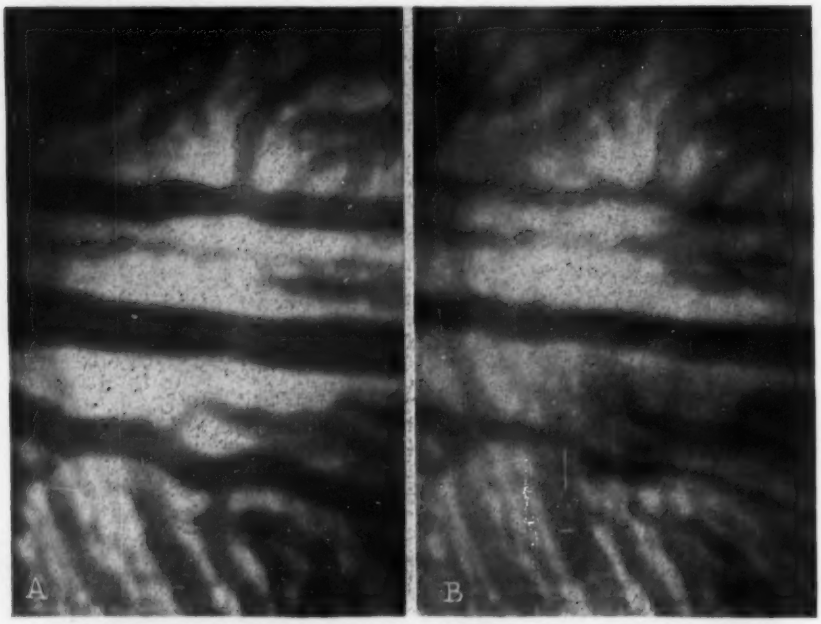

Fig. 11.—Effect of local instillation of croton oil on the caliber of the choroidal vessels. *A*, before instillation. *B*, after instillation the long and short ciliary arteries show a moderate reduction in caliber. Reduced to 58% of mag. × 40.

appeared to be a passive decrease in the caliber of the vessels. These fluctuations were interpreted as indicating adjustments in the vascular bed, subordinated to a redistribution of the blood toward areas with a more dependent position, as a result of which a decrease of the flow through the eye occurs.

It should be strongly emphasized that the lack of dilatation of the choroidal vessels in our present investigation could be due to the experimental conditions (proptosis of the eye, dehydration of sclera, insertion of plastic disc in suprachoroidal space, etc.), and that the absence of response to this type of drugs could be due to maximal dilatation that existed from the beginning of the studies.

Veins and capillaries: As was previously reported by Leopold,[41] in the present investigation we did not observe any effect of the various drugs on the veins that integrate or drain the choroid.

The capillaries and terminal vessels were in general poorly visualized in living animals, and the present observations did not shed any light on the behavior of these structures.

SUMMARY

The effects that the various pharmacological agents had on the choroid of living animals can be conveniently described in the following groups:

I. Agents that manifested a direct action on the choroidal vessels.

1. Epinephrine. Local instillation and intravenous and intravitreal injections of epinephrine caused a moderate vasoconstriction of the long and short posterior ciliary arteries; this reaction was more noticeable in the intraocular portion of the vessels. The constrictive effect was focal in type and gave a tortuous appearance to the vascular structures. Frequently noticed after repeated intravenous injections of epinephrine (and after arterenol and local trauma) was the passage of white masses, pliable and soft, that were carried along the circulation as emboli.

2. Arterenol. After intravenous and local administration this drug produced changes resembling those that followed the administration of epinephrine.

3. Phenylephrine. When applied locally, it produced a moderate focal constriction of the posterior ciliary vessels during their passage through the suprachoroidal space.

4. Ephedrine and methoxamine. Intravenous injection of these drugs induced slight constriction of the intraocular portion of the long ciliary artery.

5. Histamine. Local instillation of histamine was rapidly followed by a marked and uniform vasoconstriction, which affected the intraocular portion of the long and short ciliary arteries. Intravenous and intravitreal administration of the drug yielded similar changes.

6. Vasopressin (pitressin).—This drug, when applied locally, produced constriction of the long and short ciliary arteries; this was a focal type of vasoconstriction, and the portions between the constricted areas acquired a fusiform appearance. After intravenous administration this agent induced a constriction in all the choroidal arteries; it is important to note that vasopressin was the only substance to produce a narrowing of the arterioles.

7. Croton oil. When applied locally, the drug produced a moderate constriction of the intraocular portion of the long and short posterior ciliary arteries.

II. Agents that influenced the choroidal circulation only when systemic effects were noticed. The circulatory choroidal changes consisted in pallor of the vascular coat, decreased speed of flow, and pulsations at the points where the arteries perforate the sclera. On some occasions a temporary standstill of the circulation was observed, with transitory reversal of flow and passive decrease in vessel caliber.

1. Cholingeric drugs: Methacholine, carbachol, bethanechol, and pilocarpine.

2. Parasympathomimetic drugs: physostigmine, neostigmine, and isoflurophate.

3. Parasympathetic-blocking drugs: Atropine, scopolamine, and methantheline.

4. Adrenergic- and sympathetic-blocking agents: Dibenamine, tolazoline, phentolamine, piperoxan, ergotamine, ergotoxine, and ergonovine.

5. Ganglion-blocking agents: Tetraethylammonium and hexamethonium.

6. Direct vasodilators: Nicotonic acid, aminophylline, amyl nitrite, and glyceryl trinitrate.

The changes observed after administration of epinephrine were first studied in our laboratory by Dr. Alfred W. Scott.

Dr. Adolph W. Vogel made helpful suggestions in this study, and Dr. Harry Feilchenfeld assisted in the preparation of the manuscript.

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Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

SUBCLINOID ANEURYSM OF THE INTERNAL CAROTID ARTERY

SUBCLINOID or intracavernous aneurysms of the internal carotid artery are rare, producing few and unobtrusive orbital signs, which are readily missed, and, when located posteriorly in the sinus, produce only a sixth nerve paresis, usually with trigeminal signs.* The following case is of interest because of the presence of an isolated right abducens palsy of seven years' duration in a young adult which was surgically corrected three years prior to the demonstration of its aneurysmal etiology.

Right internal carotid angiogram, lateral x-ray view, demonstrating the saccular aneurysm.

REPORT OF CASE

The patient, aged 20, a white seaman of Italian extraction, was seen in consultation from the Neurology Service, U. S. Naval Hospital, Philadelphia, after being admitted to the hospital on

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From the Ophthalmology Service, U. S. Naval Hospital, Philadelphia.

The opinions or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the view of the Navy Department or the Naval Service at large.

* References 1 and 2.

Jan. 19, 1955. His complaints were of numbness beginning in the left thumb and spreading up the left arm, with involvement of the lips and tongue. This had been present about eight months, occurring in transient bouts lasting three to five minutes and associated with bifrontal headache, bitemporal constriction of the visual fields, and diplopia.

The past history revealed that at the age of 13 he had had a 10-day febrile illness with headache, vomiting, and the onset of a right internal strabismus with diplopia. The headaches and diplopia persisted after this illness. At age 17, in his home community, an ophthalmologist established a diagnosis of an abducens palsy on the right, and a recession-resection operation was performed, with a good cosmetic result.

Ophthalmologic examination in 1955 showed VOD 20/70 cc 20/20, VOS 20/20, surgical scars over the right medial and lateral rectus muscles, and a small degree of exotropia, with the crossed diplopia greatest in the field of action of the right medial rectus muscle. The visual fields and the ocular examination otherwise were normal. The neurologic examination, lumbar puncture, and electroencephalogram were within normal limits. X-rays of the skull showed a small right parasellar calcification.

In March, 1955, carotid angiography demonstrated a 2 cm., oval infraclinoid aneurysm of the right internal carotid artery near the siphon (Figure). Subsequently, Lt. N. I. Aronson (MC), U. S. N. R., of the Neurosurgical Service, performed a ligation of the artery in the neck, using a Silverstone clamp. The patient made a good postoperative recovery, and repeat angiography showed that the aneurysm had been obliterated.

COMMENT

Cerebral angiography now has a secure place in the diagnosis of neurologic diseases, particularly the vascular disorders, which can be made safely and with certainty.† Parkinson and Childe [5] advocate routine use of angiography in suspected vascular anomalies in selected cases and report no fatalities in the investigation of 200 consecutive cases.

Angiography in the case here reported made possible the establishment of the etiology of an isolated abducens palsy, with the institution of proper therapy. Close consultation between the ophthalmologist, the neurologist, and the neurosurgeon is most important in the proper management of many neuro-ophthalmologic problems.

LT. CMDR. WAYNE L. ERDBRINK (MC), U. S. N.

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Annual Reviews

OPTICS AND VISUAL PHYSIOLOGY

A Review of the Literature for 1955

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ARTICLES of special interest to be reviewed here this year include the following: Foster,[1] Presberg,[7] and Williams [28] on refraction technique and problems; Busacca [53] and Burian [54] on observation of the iris angle during accommodation; Kujus [75] on eye strain from reading; Bjork [76] on electromyography during reading; Bruell and Albee [77] on visual localization during eye movements; Linksz [82] on theoretical aspects of the horopter; Ogle [95] on vertical disparity and fusion areas in the visual cortex; Rushton and Campbell [156] on measurement of the percentage of bleached rhodopsin in the living human eye, and Granit [172] on electrophysiology.

REFRACTION

An English ophthalmologist describes methods of increasing efficiency in the "ophthalmodiagnostic process." [1] The vision test chart should contain only one or two letters per line to be read vertically. He found the duochrome refraction test quick and precise. Refracting machines were rejected in favor of trial frame and loose lenses. He estimated a saving of 50 seconds per patient by use of a variable hand prism for motility tests.

The duochrome refraction test consists of a black figure on a red background, adjacent to a similar black figure on a green background. It is used after the refraction is nearly finished, to test the spheric correction by the position of the red image, which should lie behind the retina, and the green image, which should lie in front. If the target appears sharper on the red side than it does on the green, the trial frame contains too much plus sphere. If it appears sharper on the green side, one should add plus sphere. Brinkbo [2] states that the "duochrome test appeals to the sense of color" and is poor in patients with color blindness. This is not true. Chromatic aberration exists in all human eyes, and the test should work in all patients who can see 20/25 or better, whether or not they are red-green blind.

In various types of normal and pathological eyes, retinoscopy was found superior to the refractionometer.*

Binocular fusion during refraction should be helpful in several ways. There would be a fusion lock to prevent torsional eye movement and a stabilizing effect on accommodation from the accommodation-convergence reflex. A modification [5] of the Turville method is described in which dissociation of the line of type being used for fixation is accomplished by a sagittal screen between the eyes.

When the crossed cylinder is used properly for testing the axis or amount of cylinder, the conoid of Sturm remains bisected at the circle of least confusion by

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* References 3 and 4.

the retina.[6] When the cross cylinder is flipped for testing power, the interval between the two foci will first lengthen and then shorten. "One of the worst mistakes . . . is to perform the tests with the eye fogged. This places the circle of least confusion either in front of or behind the retina and produces both size and shape changes in the letter or letters viewed during the test."

Refraction produced psychic trauma, frustration, and doubt in many tense nervous patients.[7] Patients may take the matter too seriously and try too hard. Offering a patient the choice of plus or minus 0.25 sphere may result in more and more plus until test letters are illegible. One should not refract more rapidly than a patient can discriminate. The trial-frame method is superior.

Changes in refraction due to ocular operations[8] and to systemic diseases, like diabetes,[9] are discussed. In diabetes, refraction may change from 0 to —2.25 or to +3.25 D., depending on the hydration of the lens or vitreous. Photographs taken through the biomicroscope showed changes in refractility of superficial parts of the lens as compared with the nucleus, but no apparent shift of lens position.

In the fogging method of refraction, the plus sphere may stimulate instead of relax accommodation.[10] For relaxation of accommodation, there must be a visible distant object. Looking through excess plus sphere may result in measurable esophoria.

MYOPIA

A study of Angmagssalik Eskimos[11] included anthropological as well as ophthalmological findings. Only small infants (6.6% of the population) failed to get a cycloplegic refraction. A total of 1405 eyes were found free of pathology. Of these, 282 showed high inverse astigmatism, but there was no myopia. The average refraction was found to be +0.10 D. Since Asiatic populations have a high percentage of myopia, it was concluded that these Eskimos did not have Asiatic ancestors. According to the Steiger refraction theory, a genetically pure group like this should have a distribution curve without the hypermetropic skew. The only similar group nearly free of myopia was that reported from Africa by Holm in 1937.

In visual field studies of 100 highly myopic eyes,[12] 24% showed abnormalities such as centrocecal or ring scotomata. The blind spots were frequently enlarged, due to myopic conus.

An Italian author[13] found that myopic patients had less than average amplitude of accommodation and earlier presbyopia, regardless of the degree of myopia. Most reports say that myopes with full correction since childhood have normal accommodation and presbyopia. It has been said[14] that Mediterranean people become presbyopic at the age of 40, whereas Scandinavians wait until age 48.

In a discussion of routine refraction, Cowan[15] states that children with myopia should be fully corrected for distance. The under- and overcorrection of myopia, in his opinion, would not affect the progress of the myopia. It gives one a rather helpless feeling about myopia to believe that it is purely genetic, I find. Optometrists use undercorrection, fusion and other visual exercises, base-in prisms, and even bifocals to relax accommodation, although there are no well-controlled studies showing noticeable benefits. Parents of myopic children find positive treatment more appealing than negative. Myopia has been treated surgically by the Sato method,[16] by cataract extraction,[17] and by scleral shortening.†

† References 18-21.

ASTIGMATISM AND OCULAR TORSION

The effect of glasses correcting oblique astigmatism to create cyclophoria is discussed.‡ Such cyclophoria follows attempted fusion of retinal images made asymmetric by astigmatism. We are careful to warn the patient of apparent floor and wall tilt when the axis of astigmatism is changed.

If the cyclophoria and floor tilt are actually due to the fusion of asymmetric images on the retinas, making the images symmetric by aniseikonic lenses should be the perfect solution. I have tried this on several occasions, with doubtful results. The late J. I. Pascal said [24] that patients cannot wear glasses correcting high astigmatism because only in primary gaze are they right. On looking down or up, or on tilting the head to one side, the eyes undergo torsion but the glasses do not. Perhaps contact lenses should be tried, since they would eliminate aniseikonia and the effect of torsion. It is occasionally helpful to prescribe two pairs of glasses, one with axes determined at distance, and a second with axes determined at near. Use of undercorrection by spherical equivalents has been necessary in some cases.

The articles on ocular torsion in oblique gaze § show better agreement on spatial concepts and terminology this year.

APHAKIA

In the correction of aphakia, there must be close understanding between the refractionist and the optician.[28] The effective power of lenses in the trial frame often differs as much as 0.50 D. from that in the finished glasses, owing to a difference in vertex distance and lens form. It is not good to "grind off" or "resurface" a lens, because the edge may become thin and weak and the surface aspheric. Another source of error in glasses for aphakia may come from a difference in pantoscopic tilt to alter the astigmatism.

Most errors can be prevented by putting temporary glasses on the newly aphakic patient, then two months later doing a refraction over the temporary glasses.[29] This is not too difficult in practice and does certainly control the vertex distance and lens form and pantoscopic tilt.

Aphakia lenses should be small, perhaps 43 mm. in diameter, to decrease weight. The distance power should be decentered in from 1 to 2 mm., and the segments need additional decentration of 2.5 mm. or more. Aphakia lenses should have a plano-minus cylinder on the rear surface, rather than the —3.00 D. sphere, which puts the cylinder in front, too far from the eye. Light-weight lenticular bifocals are often no real advantage over thin-edged Kryptok lenses shaped this way. The latter are much more economical.

Retinoscopy is often helpful in the refraction of aphakes, but it should be done through precision type lenses.[30] In blue or violet light, the visual thresholds of an aphakic eye are superior to the normal by about 1 log unit,[31] because of lens fluorescence and scatter.

RELATIONS WITH OPTOMETRY

"Refraction and the prescribing of glasses is an integral part of ophthalmology, for a number of obvious and cogent reasons," says Derrick Vail.[32] In several states, legislation has been proposed which would restrict the practice of refraction by

‡ References 22 and 23.

§ References 25-27.

ophthalmologists, or the prescriptions through dispensing opticians. Resolutions [33] were made concerning the ethics of instruction or employment of optometrists by ophthalmologists.

CONTACT LENSES

Contact lenses are becoming increasingly useful.‖ Ellerbrock reports the case of a school teacher aged 37 who had Bell's palsy.[36] She could not blink enough to prevent drying of the cornea. Voluntary lid closure caused an ugly grimace; so she would close the eye with her finger every few minutes. In this instance, contact lenses provided a cure.

Contact lenses [37] are used in treatment of scarred corneas, keratoconus, buphthalmos, and nebulae, and in unilateral aphakia. For albinism and aniridia they may be tinted. For covering deformity they may be opaque. Contact lenses are in use for protection of healing corneal transplants or to hold separate symblepharon bands newly operated on. They are useful in gonioscopy. One writer [38] states that in keratoconus the lens should touch the corneal apex. Except for the new self-ventilating type, contact lenses may interfere with corneal metabolism.[39]

MAGNIFIERS

A projection magnifier has appeared in mass production which promises benefit to those with defective vision. I have shown it to several patients in my office, to whom it seemed effective and convenient. It would enable those with vision between 20/70 and 20/400 to read books and newspapers. It is stronger in power than telescopic or microscopic spectacles and has the advantage of no image movement, unrestricted visual field, and unrestricted head movement.

It is well known that training and patience are required for telescopic or microscopic spectacles.[40] Even after many months, patients continue in slow progress. They prefer lightness of weight and breadth of visual field to high magnification.[41] The various types of magnifying glasses available are described.¶

ANISEIKONIA

Adelbert Ames Jr., the discoverer of the clinical entity in which the two ocular images are unequal in size or shape, was honored by the award by the Optical Society of America of the Tillyer Medal in April, 1955. The citation stated that his work and enthusiasm was responsible for much of the research in physiological optics in this country in the past 25 years. His death, on July 3, 1955, is deeply regretted.[45]

The measurement and the indications for treatment of aniseikonia are gradually becoming better known. There are now 29 ophthalmologists and 53 optometrists who own the space eikonometer. The test is available in nine university ophthalmological departments. While patients with aniseikonia are admittedly rare, and perhaps unpleasant, I have not known anyone with experience in the treatment by iseikonic lenses to abandon the method. The results in some patients are as dramatic as that following cataract extraction.

A new clinical manual on aniseikonia was written this year by Bannon,[46] who was one of the original Dartmouth Eye Institute staff. The booklet describes in detail the course and treatment of 25 cases.

‖ References 34-35.

¶ References 42-44.

OPTICS

According to Rotter,[47] slit-lamp examination of the human retina should be done with a +50.00 D. lens placed near the cornea, instead of the —55.00 D. Hruby lens. The plus lens was said to provide a wider field and equal magnification. The optics are the same indirect ophthalmoscopy as that in the Schepens ophthalmoscope.

For students interested in simplified optical calculation, the graphic method is recommended.[48] No compound fractions or long division is required. Models illustrating the path of light rays through the Maddox rod are of interest.[49] An instrument for measurement of the marginal power and astigmatism of ophthalmic lenses is described.[50] These measurements frequently differ from those in the center. Several years ago W. B. Rayton patented an ophthalmic lens which was calculated for the least error in marginal power and astigmatism at a visual fixation distance of 1 meter, instead of the usual infinity. Such lenses have been commercially available for several years. Theoretically, they are quite superior.[51]

ACCOMMODATION

The human crystalline lens stiffens in presbyopia in the shape which is natural for distance vision, in which the zonules are tight. In this, no one has convincingly refuted the Helmholtz theory. Fincham [52] states that, whereas a youth may exert 2 ciliary-muscle-contraction units to accommodate 2 D., the presbyope may have to exert 15 units. Fincham used a haploscope in which accommodation could be produced by enforcing convergence, and then measured by his refractometer. Variations in such accommodation produced by weak local physostigmine or homatropine indicated that in all conditions at all ages the amount of accommodation per degree of convergence remained a straight-line graph.

In a young man with a normal eye except for iridectomy, gonioscopy revealed physiological changes during accommodation.[53] Physostigmine made the ciliary body swell and move anteriorly, putting the zonules on a stretch over a wide base, not parallel, as they appeared with atropine. Physostigmine made the lens more globular and the iris angle narrow. Atropine flattened the lens, which seemed to move toward the vitreous, while the ciliary body moved back. The tips of the ciliary processes moved toward the lens.

Burian and Allen [54] observed accommodative changes by gonioscope and slit lamp in 20 normal eyes. In accommodation, the pupil contracted and the adjacent iris bulged forward, while the middle zones of the iris bowed back. No definite change in position of ciliary body or trabeculum could be seen. In accommodation, the vitreous face near the zonules bowed back or forward at the hyaloideocapsular ligament, indicating looseness of the vitreous face and zonules. Such studies are not satisfactory in eyes in which the lens is subluxated or otherwise abnormal.[55]

Infrared photography can be used to record accommodative lens changes.[56] Aged cats may have other blessings in addition to nine lives, since no sign of presbyopia could be found.[57] The feline lens is exceedingly translucent compared with the human.[58]

There was no consistent accommodative change after caloric or rotatory vestibular stimulation.[59] Anatomical and physiological studies of the dog ciliary muscles indicated sympathetic innervation and intricate detail.[60] The amplitude of accommodation of South Africans was below average at all ages.[61] Determina-

tions of the accommodation-convergence ratio are not satisfactory by means of the Maddox rod, and measurements should be made in a haploscope.[62]

In use to test accommodation, a gray ring on a background half white and half black showed a distinct shift in contrast in the gray the instant a refractive blur occurred.[63] Cyclopentylate (Cyclogyl) 1% should replace home-administered atropine for refraction, according to two authors.# If the eyes cannot be examined within 30 minutes, it is important to add another drop. It is recommended [65] that cyclopentylate be followed by 1% pilocarpine to speed recovery. This procedure is, of course, harmless, but I should tell the patient that the pulling and twitching will not "ruin the eyes."

READING

The average person in reading makes about eight fixation pauses per line. For each fixation, there is a make and break of fusion.[66] Therefore, to read faster, one should take training to shorten fusion time and to increase Panum's fusional areas. About 20% increase in reading rate was accomplished by improving speed of comprehension by the tachistoscope. To reduce the number of fixations per line, one can learn to use for fixation cones farther and farther from the center of the fovea. Patients may have no complaints, yet benefit in reading rate by glasses [67] and better lighting.[68]

To avoid friction between school authorities and parents,* one should be careful to tell the parents of children referred unnecessarily that the school did right in sending them. Especially are the stereoscopic screening instruments inadequate and unsuitable for school children.

A simple vision test to be administered by the school nurse included visual acuity on the Snellen chart, acuity through a +1.75 sphere for hypermetropia, and use of the Worth four-dot test for muscle balance and fusion.[69] In a series of 4662 children, 55.8% failed the Massachusetts test the first time.[70] Of these, 20% failed on retest. The test was designed to appear familiar and to appeal to small children.

Partially sighted or highly myopic children who cannot keep up with regular classes should learn reading in special classes.† In some other subjects, they should rejoin the normal students. Various aids, such as magnifiers, fluorescent indirectly lighted blackboards, and bulletin typewriters, are mentioned. Refractive errors appear to have little statistical influence on the reading achievement of pupils who do passing work.[74]

In an intriguing account of the development of writing in the second and third millenium before Christ, Kujus describes "boustrophedon" writing by the Greeks.[75] The term means plowing the writing both right and left, as by oxen in a field. To avoid the jerk back at the beginning of each new line should "improve the intellect, support the soul, and prevent detached retina." Boustrophedon writing would favor modern methods of teaching reading by flash cards, where one visualizes the word, not the letters.

ELECTROMYOGRAMS

Electromyograms are reported by Bjork on 10 normal subjects during reading.[76] In the horizontal rectus muscles were placed fine monopolar needle electrodes activating a double-beam oscillograph recording on running film. It was possible

References 64-65.
* References 69-71.
† References 72-73.

to show reciprocal agonist and antagonist action of the internal and external rectus muscles. In reading, saccadic movements seen resembled the fast phase in opticokinetic nystagmus tracings. During reading, the right lateral rectus shows short rapid bursts of electrical activity, increasing at the same time that the bursts of the medial rectus are inhibited. The inhibition phase shows less than base-line activity, with fixed gaze. Between the spurts are fixation pauses, during which the tracing resembles the base-line activity. All the way across a line of print, the activity of opposing recti maintains strict inverse proportion. The backsweep for the next line is an episode of strong activity of levorotators with inhibition of dextrorotators. The time for eye movements and the return sweep is only 5% to 10% of the reading time. For prose, each fixation pause is about 0.22 second.

SPACE PERCEPTION

During ocular movements, retinal images of buildings, streets, etc., move across the retina. This image movement is not consciously perceived unless the eye movement was involuntary. Retinal image movement produced by a voluntary eye movement is compensated before perception occurs. Bruell and Albee [77] attribute this to proprioceptive innervations in the oculorotary muscles and illustrate it with an ingenious coordinate system. They found in vestibular nystagmus and in homonymous hemianopsia that the foveas habitually take positions to one side of zero, even though foveal vision is normal. This phase of vision needs further study, because it might improve the ability to distinguish fixed from moving objects in highway traffic.

The terminology and some problems and pitfalls of visual space perception are well reviewed.[78] The texture of background and surround plays an important part in space perception.‡ The space within which a target of fixed size can be seen as in visual fields at various distances is surprisingly cigar-shaped.[81]

THE HOROPTER

The horopter concept is necessary for full understanding of binocular fusion, stereopsis, fixation disparity, and physiological diplopia. Linksz,[82] in 69 pages, explores thoroughly the theoretical aspects. He defines the horopter as the sum of all loci in visible space which one can bifixate while maintaining a constantly (usually symmetric) angle of convergence. To me, the term "bifixate" suggests foveal lines, but Linksz means all corresponding points and lines. Each point on the horopter is the position in space where corresponding lines would theoretically cross or touch when drawn through the ocular nodal points.

When horopters are constructed from sets of corresponding points, all having equal angular separation on the retina, the points of foveal fixation are restricted in number. The number of such horopters is great in near vision, but they are separated by rapidly increasing distances toward infinity. The distances would be in proportion to the loss of stereopsis with far gaze. In gaze upward or downward at each fixation distance, the horopter becomes a toric curved surface. Slight modifications occur in oblique gaze, with concepts closely related to the "so-called laws" of Listing and Donders.

Individual variations in the shape of the subjective horopter depend on the distribution of direction values perceived in equal units of temporal compared with nasal retina. Linksz points out that there can be no fixed direction value (the

‡ References 79-80.

local sign of Hering) for each retinal element, because the whole set changes for each fixation distance. He therefore emphasizes that each retinal element has no innate sense for direction in an egocentric system. One must not jump to the conclusion, however, that the subjective horopter at a fixed convergence will vary from year to year. This has been measured, and, like aniseikonia, is consistent in repeated tests and does vary in a predictable way with changes in refraction.

If the horopter shape at a given distance is fixed in early childhood, and the direction values of retinal elements for that distance remain the same throughout life, one can explain the characteristic concave horopter shape in myopic subjects by the stretching and separation of retinal elements at the posterior pole between the fovea and the disc. Of 856 people, tested on the horopter instrument, 173 were myopic and showed the concavity.[83] Some emmetropic persons show some degree of concavity, which can usually be correlated with signs of retinal stretching (conus). Similar findings in 50 students on the Zeiss horopter instrument are reported.[84] Another paper seemed difficult to me because of constant reference to the Cyclopean eye.[85]

While most authorities believe in a stable monocular retinal direction sense, Brown [86] bases his contrary belief on partition experiments performed in complete darkness. While fixing a central vertical line, his subjects were unable to place another variable line at a distance to the right subjectively equidistant from fixation to another line in the left field. In the light, such partition of direction value of nasal and temporal retina showed a "uniform overestimation" of the medial segment in 53 adults and 88 children.[87] I suspect that darkness interferes with subjective estimation of distance of the various lines from the eye. They would all have to appear to be in a frontal plane for partition experiments to be repeatable.

There is also a reported overestimation of vertical distances as compared with horizontal distances.[88] Possible causes listed are physiological nystagmus, Koffka's "spatial stress," or innervation differences for vertical as compared with horizontal eye movements.

There were two studies of fixation disparity, which is a phenomenon of retinal slip with heterophoria.§

STEREOPSIS

A new instrument consists of a precision haploscope with a reticle reflex sight for measurements on a sensitive dial.[91] It is well adapted to refined measurements of stereoscopic acuity, fixation disparity, visual acuity in various directions of gaze, and fusional amplitudes.

The distance limit of stereopsis (not depth perception) was calculated from the interpupillary distance and the diameter of a foveal cone to be about 300 meters.[92] When measured, the limit was found to be more like 200 meters. Airplane pilots very likely depend chiefly on monocular distance clues for landing. Airfields should be uniform in appearance and should have a certain familiar grid pattern. An Army team made enormous Howard-Dolman type test objects for use at distances of 200, 750, and 1500 ft. (61, 228, 457 meters).[93] On flat arctic and desert terrain, depth perception was found to be 100% finer than was expected from stereopsis alone. Monocular tests at the same time frequently gave nearly equal results. Obviously, the test conditions did not exclude monocular clues.

When two vertical line targets were varied in angular separation from the subject, within 50 degrees the stereoacuity was found to decrease with separation.[94]

§ References 89-90.

At 66 degrees, the convergence eye movements appeared as equally valid as clues to depth perception as did stereoscopic disparity. The target luminance seemed relatively unimportant as long as it remained equal on the two lines.

Stereopsis has been believed to be limited to objects seen in horizontal disparity within Panum's fusional areas. Half-images in physiological diplopia were believed to have no depth clue. Last year, Ogle showed this in error. This year, he has shown under certain conditions that in the presence of diplopia in vertical half-images there is still some stereoscopic clue to depth.[95] He used a horizontal fixation line to maintain fusion while observing in peripheral vision a point of light. The point of light was seen binocularly, but the image for one eye could be moved horizontally to create apparent sagittal forward and backward movement, but could also be moved vertically toward and beyond diplopia.

Such vertical disparity can be physiological for near oblique gaze. It is interesting that the visual cortex has developed fusion areas to make use of this type of disparity for depth perception.

Those who habitually suppress one eye were found unsuitable even after visual training for stereoscopic photographic interpretation.[96] The present knowledge of binocular vision was summarized in a review.[97]

THE PULFRICH EFFECT

The Pulfrich effect is a binocular phenomenon in which a pendulum swinging in a frontal plane appears to describe an ellipse when observed with a dark glass before one eye. This has been attributed to the time lag in visual perception of the darker image.[98] Katz and Schwartz [99] reported an apparent Pulfrich effect in the absence of binocular disparity.

VISION AND TRAFFIC SAFETY

Illusions due to a discrepancy in actual and apparent object size cause a sense of insecurity and confusion in traffic.[100] While practice and experience helps, we might drive more carefully if we were more aware of our errors of perception. Various experiments in the effect of size and shape on depth perception were reported.‖

Motion perception was measured by a gradual increase in target motion until discovered, or by gradually increasing the target light intensity.[105] At middle speeds, motion perception was considered a single sensory event, in which intensity multiplied by time is constant. The threshold also depended on a third factor—the presence of a stationary object in the field for comparison.¶

The night-driving hazard of any amount of color in automobile windshields was confirmed by Haber.[108] The loss of visibility through green glass was particularly dangerous at distances under 200 ft., where visibility decreased as much as 45%. This occurred in twilight, as well as darkness, and was particularly bad with the headlights depressed for passing. "A reconsideration of the 70% minimum transmittance requirement for windshields in the American Safety Code Z26.1-1950 was recommended."

ENTOPTIC PHENOMENA

"Haidinger brushes" and other entoptic phenomena were altered before any other sign of certain diseases, like central angiospastic retinopathy.[109] Circular polarized light can be demonstrated in human eyes by means of Haidinger brushes.[110]

‖ References 101-104.

¶ References 106-107.

VISUAL ACUITY

There is need for a test of visual acuity which is quick, accurate, objective, and expressed in percent.[111] In schools, factories, etc., any discrepancy in visual acuity as compared with past readings would then indicate disease or a need for glasses. Perhaps the optokinetic nystagmus test[112] will reach a stage approaching this. When an eye being tested looks at a rotating cylinder with vertical stripes, rhythmic involuntary eye movements occur which can be recorded electrically or photographically. The nystagmus has characteristic frequency, amplitude, and peak duration. When the stripes move by at rates from 8 to 111 per minute, the eye follows up to a certain threshold, at which the nystagmus wave form breaks into a period phasic sinus-like curve.

A series of 212 eyes were tested[113] representing all degrees of visual impairment. Optokinetic nystagmus acuity showed excellent precision and repeatability, equal at the 1/50 and at the 5/4 level of visual acuity. A reciprocating target seemed superior to the rotating drum.[114]

Visual acuity tested under a range of light intensities with or without glare seemed valuable in office practice,[115] especially in the interpretation of complaints. The contrast in background intensity is an important cause of error in testing visual acuity.[116] Contrast of letters and immediate background should be maximum, but that of the screen or card with the surrounding wall should be only about 5%. This means that the refraction range should not be a matte black, but, rather, should be light in tint.

The "checkerboard" acuity target, so widely used in the armed forces, was designed to eliminate the factor of intelligence and experience in visual acuity testing.[117] There are sets of four diamonds for each acuity level. One diamond in each set must be identified as different; it consists of lines instead of checkerboard. When the set has a black border, a normal eye can distinguish 12 seconds of arc (compared with the classic 1 minute). This acuity refers not so much to the diameter of a retinal cone as it does to the diameter of blur circles on the retina.[118]

If visual acuity testing is to be precise, the time of target exposure must be controlled.[119] We usually allow unlimited time, and some patients seem to take forever. In office practice this seems necessary.

Vilter[120] made cone counts to determine the density of various parts of the macula of a human 20 years of age. There were 50% more cones in the lower than in the upper half of the fovea. He concludes that foveal acuity is determined more by cone density than by cone quality, size, resting state, interaction, or the like. His work was confirmed in tests of resolving power of various macular areas.[121] The path of development of central scotomata was not along anatomical nerve fiber lines, but seemed related more to gravity, being arcuate below.[122] Repeated central field studies in seven cases gave rise to a theory involving tissue fluid flow between the fovea and the disc, which was most typical in glaucoma.

COLOR

We are concerned with the color of food, clothing, and shelter—but also that of automobiles and traffic lights. Since color distinguishes danger signals on land, sea, and air, the incidence of anomalies of color vision must be considered in their design. In a group of 1000 boys 10 years of age, 90 failed ordinary pseudoisochromatic test charts.[123] Of these, 14 made mistakes in interpreting red and

green traffic lights. It was concluded that adults with such color vision must learn to interpret such lights by other than color clues. Larger, brighter traffic signals helped.#

For testing color vision, the anomaloscope seemed superior to pseudoisochromatic plates.* The instrument requires that one mix different parts of red and green light until the combination matches a constant yellow. If the percentage selected varies from average, the subject has poor red-green discrimination. The Florkontrastprobe[131] has added a second pair, combining blue and yellow.

Of several brands of pseudoisochromatic plates, results on 100 normals and 100 abnormals showed the Boström IIB and the Boström-Kugelberg to be superior.[132] The Ishihara plates failed 7 normals and passed 20 defectives. The A. O. H-R-R plates failed 5 normals and passed 37 defectives. The Boström plates failed four normals and passed four defectives.

The term "congenital achromatopsia" is not correct, because such persons can discriminate blue by rod vision.[133] They probably have no cone function. A preferable term suggested was "anomalous dichromatism." Tests of the color vision of 35 carriers of protanomaly, protanopia, deuteranomaly, and deuteranopia seemed perfectly normal except for irregularities of the spectral luminosity curve.[134] The contribution of red, green, and blue receptors to achromatic brightness is discussed.

Color matching depends on the color of light to which the eyes are adapted.[135] The yellow component is very important to hue discrimination in those with anomalous color vision.[136] Slight defects in color vision, particularly diminished sensitivity to green in older persons, was attributed to yellow lens changes or macular pigment changes.†

The tristimulus color theory indicates the existence of at least four basic color excitations according to mathematical considerations.‡ The effect of the distribution of color receptors in the fovea and of chromatic aberration to cause shifts in fixation direction were studied.[141] According to an opponent-colors theory,§ pairs of colors may produce a neutral response due to cancellation of equal but opposite nerve impulses.

Studies of luminosity curves in children were reported to show evidence that cones mature before rods.[144] This is contrary to the histological evidence. The authors obtained luminosity curves in newborn infants.

Positive after-images appear immediately after withdrawal of the stimulus and are of the same color. Negative after-images are delayed and are considered perfectly complementary. Helmholtz thus concluded that the complement of yellow is blue, not violet, as artists said. Complementary colors in after-images were matched within one step on the Munsell color scale.[145] The differences compared with complementary colors established additively were chiefly in the orange-blue. There were some individual differences.

NIGHT VISION

Because of the accommodation-convergence reflex, it might be expected that a change in heterophoria would accompany night myopia. Of nine dark-adapted

References 123-126.
* References 127-130.
† References 137-138.
‡ References 139-140.
§ References 142-143.

subjects, all showed involuntary accommodation and esophoria.[146] There was no correlation, however, with the amount of night myopia or with the heterophoria measured in the usual way.

The ability to see at reduced levels of illumination depends on the age.[147] For every 13 years, the intensity of illumination must be doubled to be just detectable by the dark-adapted eye. Pupil size was controlled by use of 3 mm. artificial pupils in 188 subjects. The bad effect on vision through green windshields at night is mentioned.

The ability of the dark-adapted eye to perceive x-rays is probably direct, and not due to fluorescence.|| The threshold with an exposure of 0.02 second was 0.5 mr. The visual pathways above the retina were insensitive. The x-rays at this dosage level caused little or no destruction of visual purple.

For maximum speed of dark adaptation, one must expose the eye to red light of 626 mμ.[151] Other wave lengths, like complete darkness, are less efficient. Dark adaptation of one eye has no effect on visual thresholds of the other.[152] The effect on dark adaptation of preexposure to ultraviolet light has been the subject of considerable controversy.[153] The dark-adaptation curve varies from day to day in the part where cone adaptation is replaced by rod adaptation.[154] The onset of rod adaptation may vary as much as two minutes, changing the threshold as much as 0.5 log unit. Bouman minimizes the photochemical factors in dark adaptation.[155]

A remarkable new technique¶ permits measurement of the percentage of rhodopsin bleached at any moment in the living human eye. The instrument puts so little light into the eye that there is no interference with dark adaptation until it is 95% complete. A 2-degree retinal area is stimulated alternately by orange and by blue-green light. When dark adaptation is complete, the rhodopsin absorbs the blue but permits reflection of the orange. This light leaves the eye through the pupil and is measured by a photocell. When the rhodopsin is fully bleached in light adaptation, both orange and blue-green are reflected, so that the light leaving the pupil is twice as great. Another instrument reported tests dark adaptation by cinematograph.[158] Some effect of melanophoric hormone on night vision is described.[159]

When an eye was preadapted to white light, any color of test object produced an equal curve. However, by preadapting an eye with monochromatic light, three different types of cone activity can be distinguished.# Scotopic vision may have a regulating center in the hypothalamus.[162] A significant number of women with nonestrogenic gynecological diseases and men with endocrine oligospermia showed defects of dark adaptation not due to vitamin A deficiency. The worst cases had tumors of the pituitary region in which the absolute threshold was raised from normal (2.5 to 3.6) to 6 microlamberts (μL).

FLICKER FUSION FREQUENCY

Flicker fusion is a very sensitive test of peripheral retinal function. A new test instrument is on the market in which the flicker frequency can be decreased automatically at a constant rate.[163] This makes the test perfectly uniform in all

|| References 148-150.

¶ References 156-157.

References 160-161.

trials. In normals, this would be a great advantage, and should be used in tests for changes in vision due to drugs or various manipulations.

Variations in the intensity of the flicker test light, or variations in the light-dark ratio made little difference in testing the flicker fields of normals and of patients with glaucoma.[164] There was a general impression on the part of the patients that a brighter light was easier to discriminate, and that the bright part of the flicker cycle should be 10% or less.

Several papers dealt with factors influencing the flicker fusion rate: acoustic stimuli, tobacco,[165] and sublingual glyceryl trinitrate (nitroglycerin).* While the results did not confirm the Krasno-Ivy findings that flicker fusion as affected by vasodilators can diagnose subclinical cardiovascular disease, the methods used in the papers were not the best. For instance, bifoveal flicker fusion rates were used. Almost invariably, foveal rates differ in the two eyes. To test a vasomotor function, it would seem more reasonable to test parts of the retina away from the fovea. This is particularly true in the use of a flicker test, in which peripheral retina is superior to foveal.

Anxiety was reported to reduce flicker fusion frequency some 5 flashes per second.[170] Alcohol and anoxia were synergistic in their effect to reduce flicker fusion.[171]

RETINAL ELECTROPHYSIOLOGY

In his new book,[172] Granit has considered chiefly visual electrophysiology, although audition and muscle reactions receive attention. Human rods and cones form groups called reception fields, the size of which depends on the degree of dark adaptation. Cones operate in small reception fields, while rods work in large fields. In the center of each field, the retinal element type is either "on" or "off," but never both. The periphery of each reception field is just the opposite.

Granit emphasized the "visual gray" sensation due to spontaneous discharges of retinal cells in the absence of stimulation. Any light stimulus causes the gray to disappear. Each receptor functions like a galvanometer, with a resting position not at zero but at 50%. The needle can move toward black or white. There is no black sensation without for comparison also white.

Granit favors the Young-Helmholtz three-color theory. The "code" for color is not in the use of labeled nerve fibers capable of transmitting only one color. The "code" appears not to be in the amplitude of a wave form along a nerve fiber; more probably it is a variation in wave frequency.

When a plastic cone restricted the area of retina stimulated to the smallest one producing any response, the number of rods involved was still at least 200,000.[173] For clinical work, it has not so far been possible to restrict the stimulating light to less than the whole retina.

The interval of time between the light stimulus and the b-wave of the electroretinogram and the b-wave of the corresponding cortical response can be determined.† In the retina, the time varies with light stimulus intensity, but this does not affect optic nerve transmission. Of 57 patients with strabismus, 36 had normal fixation with amblyopia ex anopsia of the strabismic eye. All of these had normal electroencephalographic tracings. However, of 21 who could not get foveal fixation, 4 showed pathological tracings.[176]

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* References 166-169.

† References 174-176.

In the retina there are from 4,000,000 to 7,000,000 cones and about 125,000,000 rods, and even more corresponding visual cortex cells. However, the retina communicates to the cortex through only 800,000 to 1,000,000 fibers. The synaptic net theory was developed several years ago to explain the fine grain of cortical imagery. The original papers made the idea very attractive to me, but recent ones have become mathematical.[177]

ELECTRORETINOGRAPHY

There is continued interest in clinical electroretinography. In many instances, the papers contribute to the knowledge of both physiological and pathological processes. One patient and two male carriers of choroideremia showed deficient dark adaptation and extinguished electroretinograms. This was considered evidence that both a- and b-waves originate external to the outer plexiform layer of the retina.[178]

Infants less than one week of age showed only scotopic ERG curves to flickering stimuli, but during the first few weeks of life photopic waves appeared.[179] In the human electroretinograms, there were no changes after sympathetic block or intravenous nicotinic acid, but vasodilators caused a 50% increase in amplitude of the b-wave with maximum effect in 15 minutes.[180] It was concluded that the ERG arises in the bipolar layer, where the deep capillary net lies. Others have observed this in a patient with quinine optic neuritis.‡ The b-wave did increase, but the treatment with vasodilators did not improve vision.

Tolazoline (Priscol), a vasodilator, improved the ERG in hypertension, but not in diabetes.[183] The b-wave in malignant myopia was found below 0.25 μv in about 75% of cases.[184] In total choroidal atrophy the b-wave was absent. The ERG in detached retina was not of prognostic value, because the amplitude might improve from zero to normal after surgery. While the clinical electroretinogram is still in an early stage of development, it has been of value in certain retinal and optic nerve diseases.§

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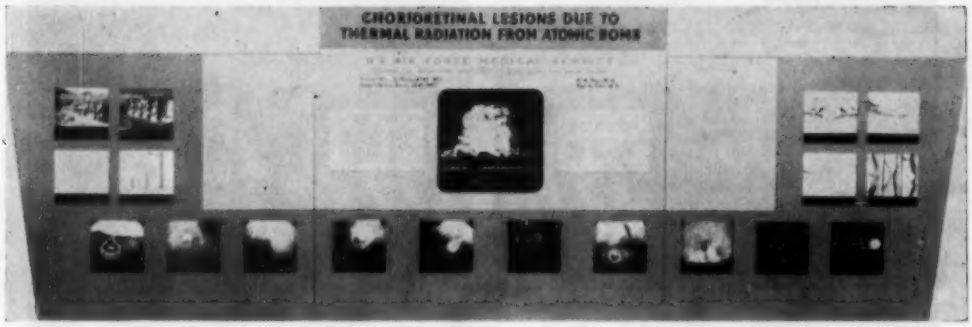

Scientific Exhibits

CHORIORETINAL LESIONS DUE TO THERMAL RADIATION FROM THE ATOMIC BOMB

COL. V. A. BYRNES (MC), U. S. A. F.; CAPT. D. V. L. BROWN (MC), U. S. A. F.; H. W. ROSE, M.D., and PAUL A. CIBIS, M.D., Randolph Field, Texas

THIS exhibit shows the chorioretinal burns produced by the energy contained in the visible and near-infrared portion of the energy spectrum when such energy is released by the detonation of an atomic bomb.

Charts show that the color temperature of the fireball at 0.0001 second is 300,000° K; at 0.01 second, 2000° K, and at 1 second, 6100° K. They also show why the eye receives about 35% of the total energy during the first 1/1000th of a second, while the skin receives only about 3% of its total dose in the same period. The other physical factors of importance, clarity of the atmosphere, and relative pupillary opening are pointed out.

The physical reason that the optical system of the eye causes these burns to be produced at very long distances is stated.

In addition, large transparencies show the experimental set-up in which 750 pigmented rabbits were utilized with the detonation of actual atomic bombs. Over 75% of these rabbits sustained retinal burns, and in at least one test 100% of the exposed rabbits sustained retinal burns to a distance of 27 miles. The longest distance available for these tests was 42 miles, and burns were sustained at this distance.

Large transparencies show the lesions produced at 2, 3, 5, 8, 10, 18, 27, and 42 miles. Rabbits under 10 miles sustained retinal explosions produced by the conversion of choroidal and retinal fluids to steam. Lesions over 10 miles were essentially plaques of coagulated tissue.

Large transparencies show the microscopic sections of the lesions produced at various distances.

U. S. School of Aviation Medicine, Randolph Air Force Base, Texas.

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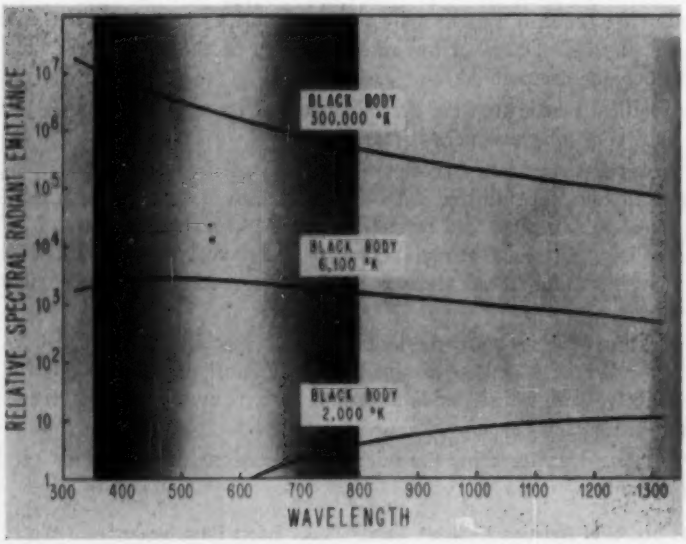
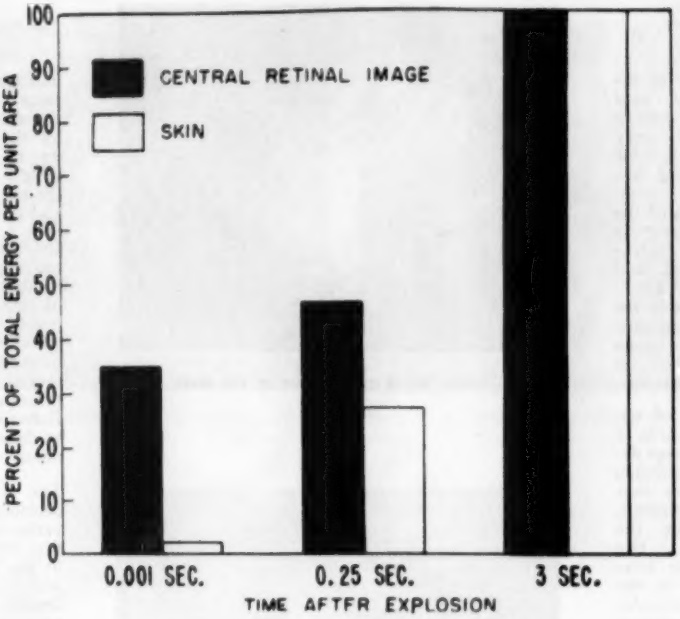
Shown as a scientific exhibit of the Section on Military Medicine at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 6-10, 1955.

Rabbits were exposed to the atomic flashes at dawn in boxes with heads fixed in such position that their visual axes were directed at the detonation point. Alarm clocks were used to awaken them just prior to detonation. Equipment shown automatically photographed the rabbits within the first 50 msec. after detonation, and before the rabbits could blink. Pigmented rabbits were used because their fundi absorb radiant energy similarly to the human.

Photographs made by means of illumination provided by atom bomb. By this method it was possible to eliminate from consideration those rabbits with closed or shaded eyes.

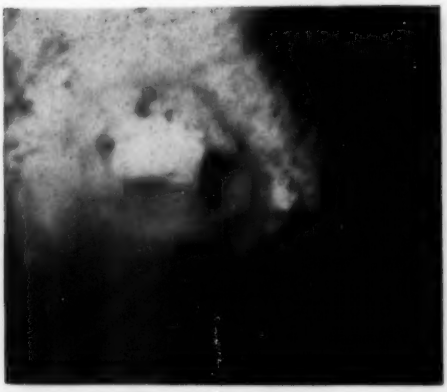


Spectral emission of black bodies of 300,000°K (at 0.0001 sec.), 6100°K (at 1 sec.), and 2000°K (at 0.01 sec.), representing three phases of the atomic fireball.



Time of incidence of certain percentages of the total thermal energy per unit area from a nominal atomic bomb for the central part of a retinal image and the skin. Thus about 35% of the total radiation arrives at the retina before protection by the blink reflex can intervene.

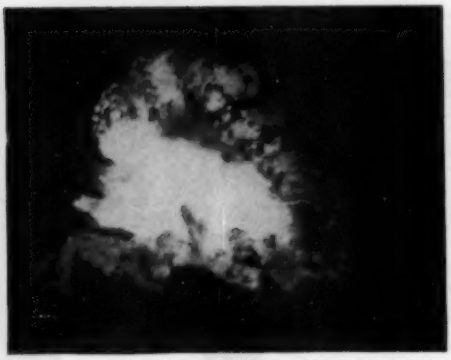
Burn produced at 2 miles from detonation point of bomb. Lesion below optic disc.



Burn produced at 3 miles from detonation point, early.

The intensity of radiant energy produced by an atomic explosion is very high. The fireball for a short period has roughly 100 times the brightness of the sun. This energy is made up of ultraviolet, infrared, and visible light. If a person is looking in the direction of an atomic detonation, an image of the fireball is formed on his retina.

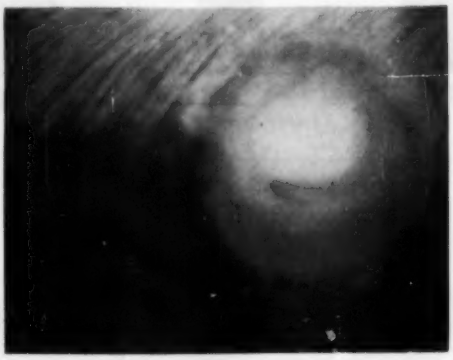
The amount of energy per unit area of this retinal image depends on the emission of energy per unit area of the fireball, attenuation by the atmosphere, the square of the relative opening of the eye, and the absorption by the ocular media. While the amount of energy falling on the eye decreases as the square of the distance, the size of the retinal image decreases by the same ratio, so that the energy per unit area remains the same (minus only the energy absorbed by the atmosphere) up to distances at which the optics of the eye form a minimal-sized image.



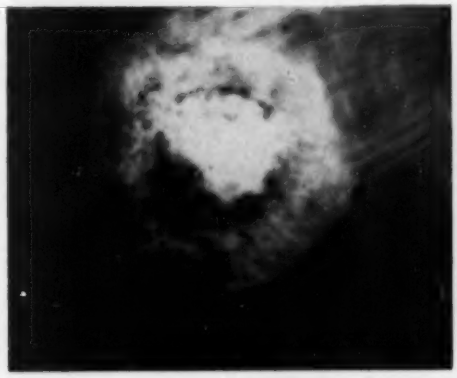
Atomic bomb used in one of the tests.

In an experiment utilizing 750 pigmented rabbits, 75% of the rabbits exposed at dawn to atomic-bomb detonations received chorioretinal burns at distances up to 15 miles. Burns were observed at distances up to 42 miles.

The visual effect of chorioretinal burns varies with the location of the injury. If in the macula, there will be a permanent scotoma and loss of visual acuity. If more peripherally located, then fiber bundle interruption and retinal detachment constitute serious hazards. A substantial burn on the optic disc may result in complete blindness.

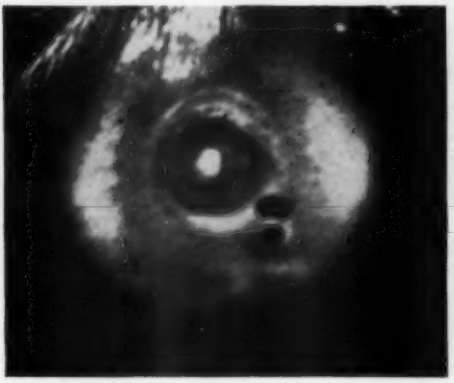


Burn at 3 miles, five hours after detonation of bomb.



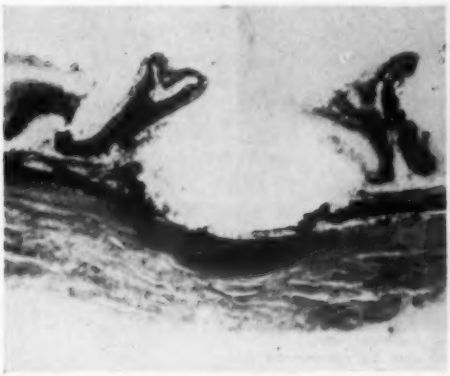
Lesion of preceding photograph four weeks after injury.

Burn produced at 5 miles from detonation point of bomb.

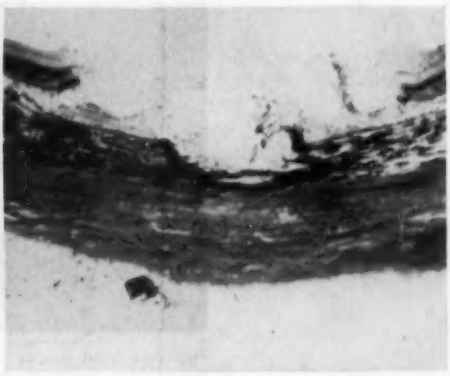


Burn produced at 8 miles from detonation point of bomb.

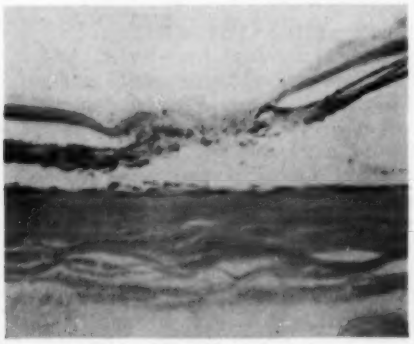
Burn produced at 10 miles from detonation point of bomb.



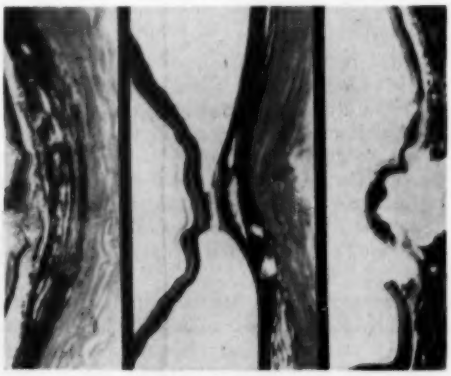
Chorioretinal and scleral lesion produced at 5 miles from detonation point of bomb. Local heating above the boiling point produced a water-vapor explosion.



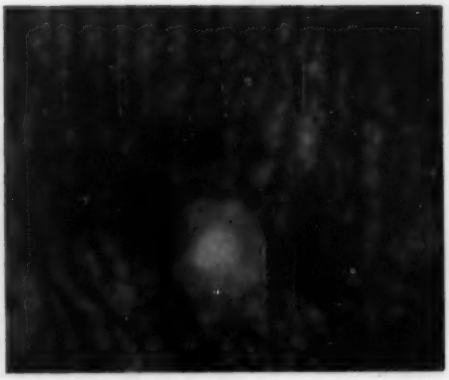
Moderate chorioretinal lesion also produced at 5 miles. Coagulation necrosis involves all layers of the retina and choroid.



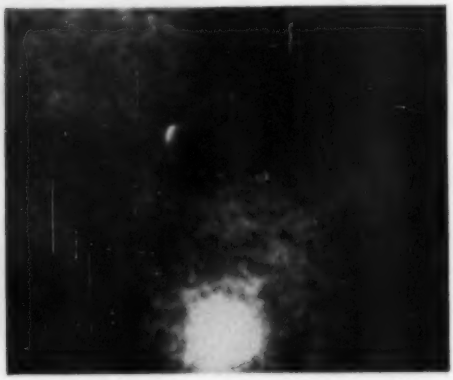
Minor lesion with main damage in pigment layer and the outer layers of the retina.



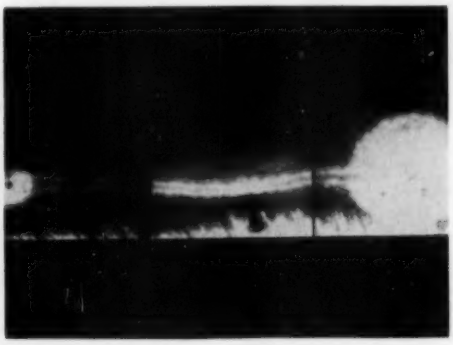
Composite histological picture referring to double lesion in the last illustration of the exhibit.



Burn produced at 18.5 miles from detonation point of bomb.



Burn produced at 42 miles from detonation point of bomb.



Interconnected double lesion due to movement of the rabbit's eye produced at 10 miles from detonation point of bomb.

News and Comment

ANNOUNCEMENTS

Public Health Service Research Grant Applications.—The U. S. Public Health Service has announced a new procedure to expedite the processing of research grant applications for those requests which do not exceed $2000 plus indirect costs and which do not ask support for more than one year. Such applications will be accepted and processed on receipt and are not therefore subject to the usual deadlines for submission prior to review.

Council recommendations can be expected on these applications within one to four months from the time of submission. These procedures do not apply for requests for supplements to existing grants.

Address all applications, as well as requests for forms or additional information, to the Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

The American Orthoptic Council Examination for Technicians.—The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in August and October, 1956.

The written examination will be nonassembled and will take place on Thursday, Aug. 23, in certain designated cities and will be proctored by assigned ophthalmologists.

The oral and practical examinations will be held on Saturday, Oct. 13, in Chicago, just preceding the meeting of the American Academy of Ophthalmology and Otolaryngology.

Application for examination will be received by the office of the Chairman of Examinations, Dr. Frank D. Costenbader, 1605 22d St., N.W., Washington 8, D. C., and must be accompanied by the examination fee of $30.

Applications will not be accepted after July 1, 1956.

Books

The Year Book of the Eye, Ear, Nose and Throat (1955-1956): **The Eye.** Edited by Derrick Vail, M.D. Price, $6.50. Pp. 471, including indices, with 121 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

The value of this excellent review of ophthalmologic literature abstracted from journals received between October, 1954, and September, 1955, is considerably enhanced over that of other, similar abstracts by virtue of the excellence with which the material has been edited. Dr. Vail has not only been able to extract the valuable points from each article which he has abstracted, but has frequently annotated his abstracts with citations from previous literature and from his own experience which are extremely helpful to the reader (and frequently lend an amusing and illuminating insight into the editor's personality, as, for example, on Page 45, where he vividly recalls Verhoeff's criticism of Squan's concept of the blind spot mechanism in strabismus).

This review of ophthalmologic literature is, therefore, a vast improvement on the usual collection of abstracts, which concern themselves only with condensations of isolated papers: It does seem a pity that one has to purchase the abstracts on the ear, nose, and throat along with the ophthalmic abstracts, especially when it seems evident that because of lack of space much of value had to be omitted in the

eye section. Perhaps some day in the future the fallacy of the accustomed association of ear, nose, and throat with the eye will be discarded in literature, as it is gradually being discarded in practice.

Our Blind Children: Growing and Learning with Them. By Berthold Lowenfeld, Ph.D. Price, $5.50. Pp. 205, including index, with a few scattered illustrations, not numbered. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1956.

For the past ten years the incidence of blindness in children has increased considerably, due to retrolental fibroplasia. As a result, all ophthalmologists are now confronted in their offices with the problem of blind children and what to tell their parents. Once the dreadful news is broken to these parents that they have the problem of bringing up a blind child, who is to give them the instruction and wise counseling which will fit them for this difficult task? It is obviously something the ophthalmologist cannot escape, and yet, unfortunately, in a busy office it is simply impossible to take more than the most meager amount of time to start the parents on their uphill fight toward guiding the development of these children. This book is a godsend for the ophthalmologist, therefore, as well as a bible for such parents.

The book is intelligently written, without any sentimentality, and yet stresses the fact that the most important factor in bringing up a blind child is the same as in the case of a normal seeing child, namely, a balanced mixture of understanding and love. The author, who is the superintendent of the California School for the Blind, writes for the parents a detailed account of the problems which they will face with the blind child. Chapter V, for example, called "Growing Toward Independence," includes expert advice on the basic fundamentals of learning to eat, toilet training, sleeping habits, learning to dress, gaining body control and learning to walk, learning to talk, play and experiences, music, and emotional growth. Chapter VI describes the emotional climate in which the child grows up and gives many helpful hints to the parents regarding their attitudes, especially where the parents have to make adjustments in their expectation that their blind child will perform in all walks of life according to the standards of seeing children.

There is much common sense in this book, and all ophthalmologists would profit by reading it themselves. One of the nicest things which an ophthalmologist could do would be to have a copy of this to give to such parents at the end of the consultation, when they learn that they are now actually to embark on the courageous task of helping their blind child live in a seeing world. No book could be better written to serve this purpose.

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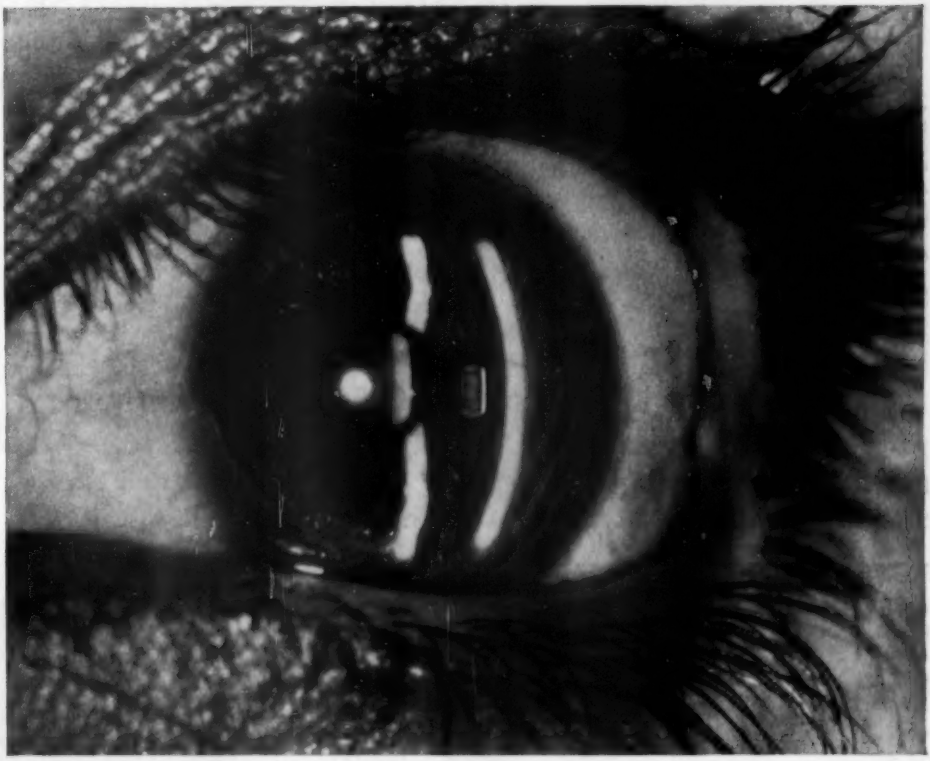

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Reference: 1. Hogan, M. J., Thygeson, P. and Kimuras, J., *Arch. Ophth.* 53:165, Feb. 1955.

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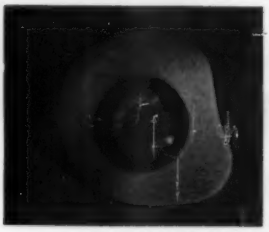

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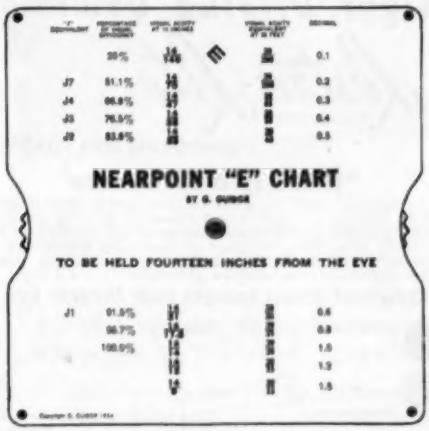

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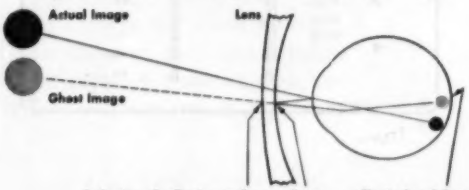

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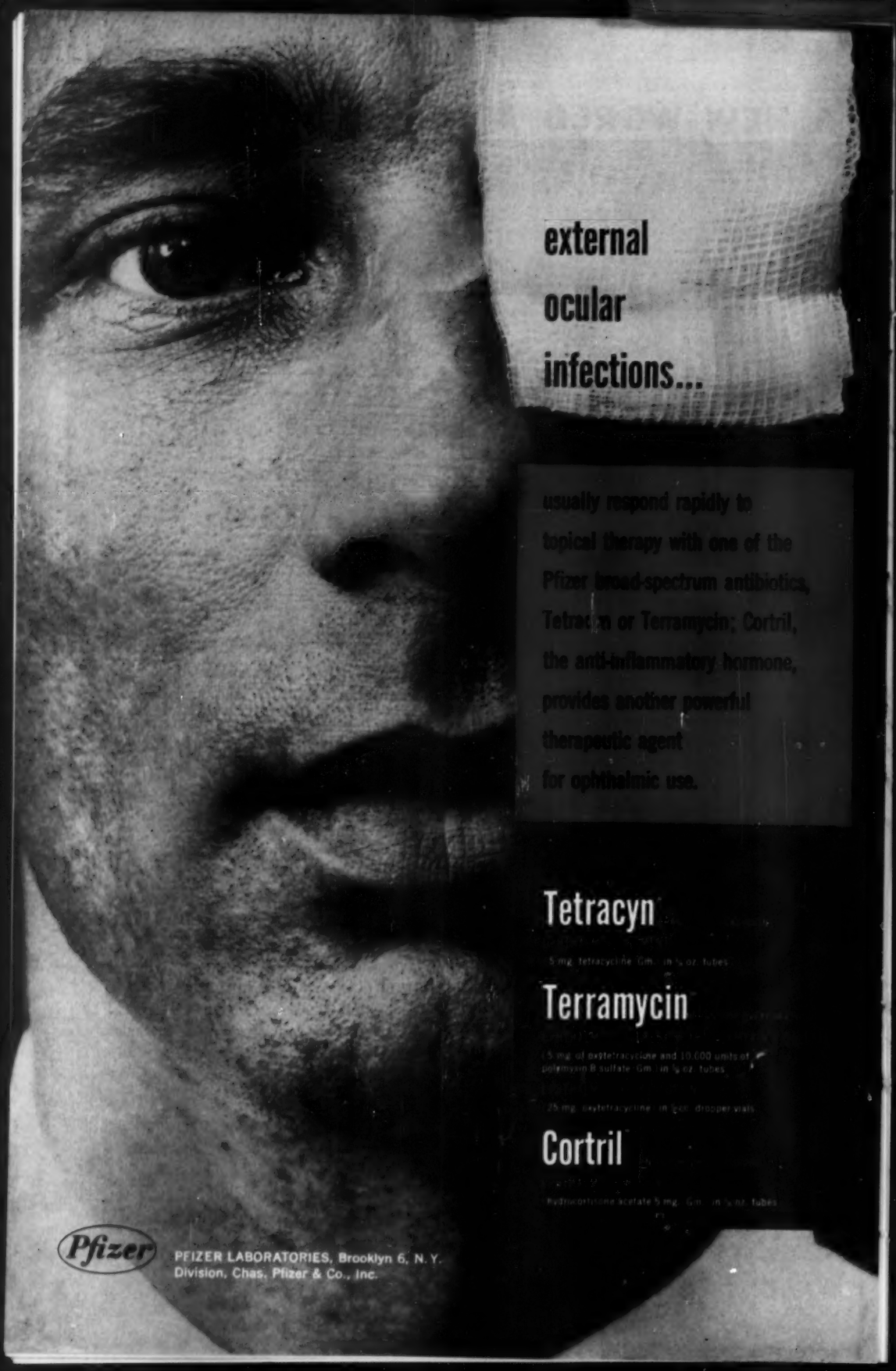
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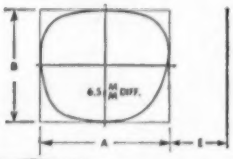

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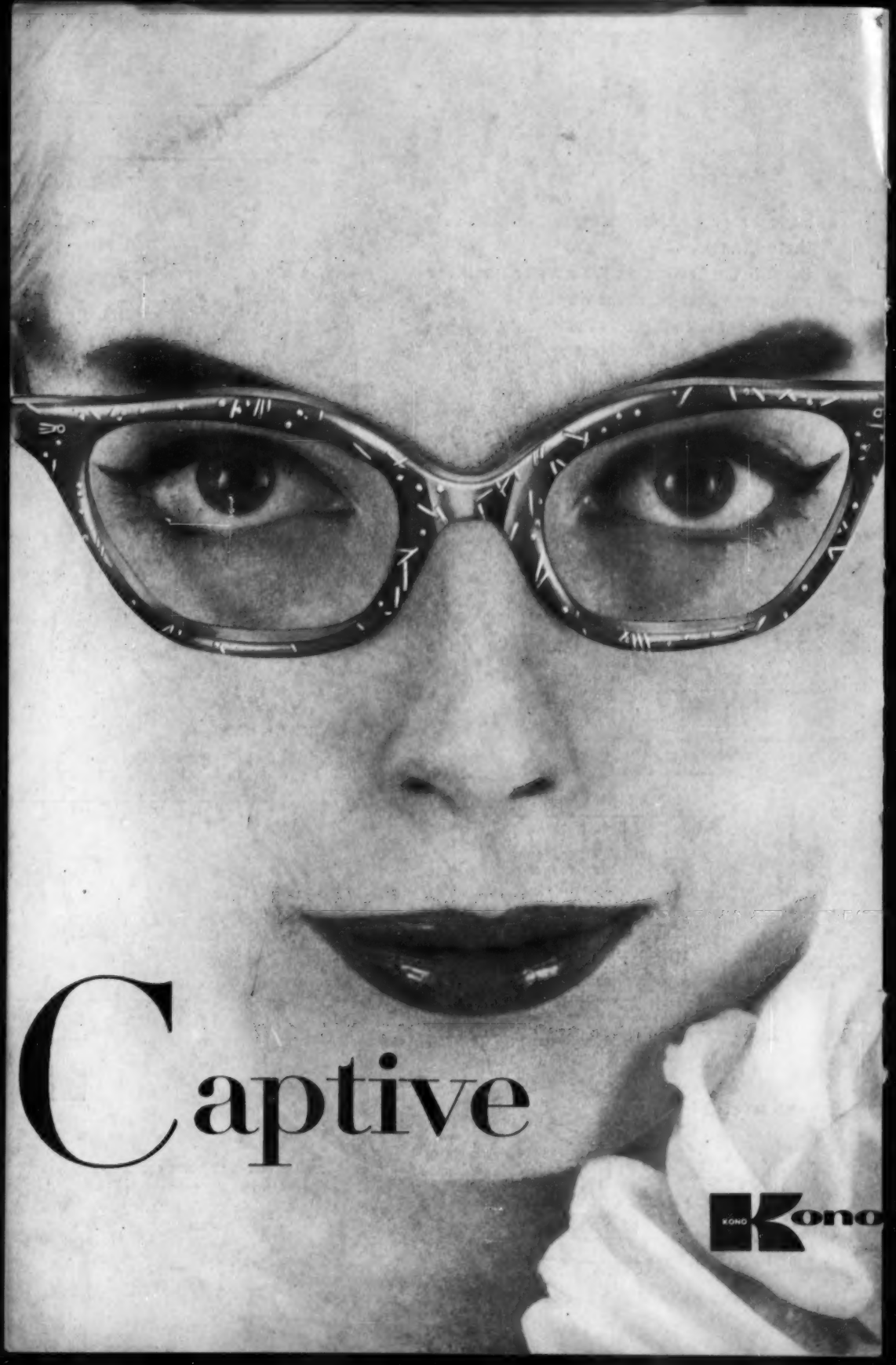
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